

Appendix A

Declaration of Hans Klingemann, M.D., Ph.D., Pursuant to 37 C.F.R. § 1.132

COPY

Appendix A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)	
)	
Hans Klingemann)	
)	
Serial No. 10/008,955)	
)	NATURAL KILLER CELL LINES AND
Filed: December 7, 2001)	METHODS OF USE
)	
Art Unit: 1644)	
)	
Patent Examiner: Ronald B. Schwadron)	
)	
Attorney Docket No. 06-129PCT/US/CIP)	
)	
Confirmation No.: 5420)	
)	

**DECLARATION OF HANS KLINGEMANN, M.D., Ph.D.
PURSUANT TO 37 C.F.R. § 1.132**

I, Hans Klingemann, M.D., Ph.D., of Boston, Massachusetts, hereby declare that:

1. All statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

2. I am the sole inventor of the modified NK-92 cells disclosed in U.S. Patent Application Serial No. 10/008,955 (hereinafter, "the '955 Application"), identified above.

COPY

3. I submit this Declaration in support of the Response To Final Office Action filed on October 15, 2008.

4. I earned my Vor-Diplom in Biology from the University of Heidelberg, Heidelberg, Germany, in 1971, and my M.D. from the University of Wurzburg Medical School, Germany, in 1976. I carried out my internship in Internal Medicine and Surgery at the University of Wurzburg Medical School, Germany, from 1977-1978 and my residency in Internal Medicine at the University of Marburg Medical School, Germany, from 1978-1984. I received additional Post-graduate training in Bone Marrow Transplant/Oncology at the Fred Hutchinson Cancer Research Center, Seattle, WA, from 1984-1986.

5. I have held academic appointments at the University of Marburg Medical School (Privat-Dozent of Medicine, 1983-1986; Professor of Medicine, 1986-1987), University of British Columbia, Vancouver, CDN (Clinical Associate Professor, 1987-1995; Clinical Professor, 1995-1997), RUSH Medical College, Chicago, IL (Coleman Foundation Professor of Medicine, 1997-2004), and TUFTS University School of Medicine, Boston, MA (Professor of Medicine, 2004-present).

6. I have also held hospital/research appointments at the following facilities: Fred Hutchinson Cancer Research Center, Seattle, WA (Research Associate, 1984-1986); University of Marburg Medical School, Germany (Attending Physician, Dept. of Medicine, 1986-1987); Vancouver Hospital and Health Sciences Center, Vancouver CDN (Active Staff, Div. Of Hematology, 1987-1997); British Columbia Cancer Agency, Vancouver CDN (Active Staff, Clinical Hematology, 1987-1997); Vancouver Hospital

COPY

and BC Cancer Center, CDN (Attending Physician, Div. Of Hematology, 1987-1997); Leukemia/Bone Marrow Transplant Program of BC (Member, 1987-1997); Terry Fox Laboratory for Hematology/Oncology, BC Cancer Research Center, Vancouver, CDN (Chief, Transplantation Biology Laboratory, 1990-1997); RUSH University Medical Center, Chicago, IL (Director, Section of Bone Marrow Transplant & Cell Therapy, 1997-2004; Medical Director, Sramek Center for Cell Engineering, 2001-2004); TUFTS-New England Medical Center, Boston, MA (Senior Investigator, Molecular Oncology Research Institute, 2005-present; Director, Bone Marrow and Hematopoietic Cell Transplant Program, 2004-present); and TUFTS-NEMC Cancer Center, Boston, MA (Director, Hematologic Malignancy Program, 2007-present).

7. Additionally, I have advised numerous trainees over the course of my academic and professional careers and have taught numerous classes, both at the undergraduate and graduate levels.

8. Over the course of my career, my research projects have included studying various basic and clinical issues in transplantation immunology covering areas such as dendritic vaccines, natural killer cell biology and mesenchymal stem cells. This translational research has resulted in over 150 publications and a variety of innovative clinical trials.

9. I have authored numerous peer-reviewed publications, review papers/editorials, non-peer reviewed publications/conference proceedings, books and book chapters, and abstracts in the fields of translational research, transplantation biology, and tumor

COPY

immunology, including a number of publications relating to natural killer cells and NK-92 cells. A list of my publications is attached hereto as Exhibit 1.

10. I have also been invited to make numerous oral presentations to a variety of audiences on topics related to the fields of translational research, transplantation biology, and tumor immunology. A list of my oral presentations is included in Exhibit 1 hereto.

11. I am also a member of the following professional associations:

- International Society of Experimental Hematology
- American Society of Hematology
- International Society for Cell Therapy
- American Society for Blood and Bone Marrow Transplantation
- American Society for Clinical Oncology.

12. Over the course of my academic and professional careers, I have received numerous awards and honors for my research contributions, including:

- Dr. Med. (Magna Cum Laude)
- Wolf Boas Research Award* by the German Society of Gastroenterology for the best Doctoral Thesis
- Habilitation (prerequisite for full professorship), University of Wurzburg Medical School, German (Ph.D. equivalent)
- German Cancer Research Foundation Fellowship

13. My education, training, laboratory research, teaching experiences, and professional activities have enabled me to develop an expertise in various specialties within the field of translational research, transplantation biology, and tumor immunology, including an expertise on natural killer cells and NK-92 cells, and their use in the treatment of cancers and viruses.

COPY

14. Based on my educational background and work experience, I consider myself to be one skilled in the arts of translational research, transplantation biology, and tumor immunology, and particularly in the area of natural killer cells and NK-92 cells.

15. I am the inventor of the modified NK-92 cell line disclosed and claimed in the '955 Application.

16. I have read and am familiar with the '955 Application as it was filed in the U.S. Patent and Trademark Office and the claims of that application as currently pending in the Response To Final Office Action filed herewith.

17. I have reviewed the following prior art references cited by the Examiner of the '955 Application in the Final Office Action mailed on April 15, 2008, and am familiar with the material disclosed therein:

(a) Gong et al., Leukemia, 1994 (hereinafter, "Gong et al."); and

(b) U.S. Patent No. 5,272,082 to Santoli et al. (hereinafter, "Santoli et al.").

18. I am one of the authors of Gong et al. and am the sole inventor of the immortal cell line, NK-92, disclosed therein.

19. I have reviewed the Final Office Action issued for the '955 Application, which was mailed on April 15, 2008 (hereinafter, "Office Action"), and which contains the following statements:

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Gong et al. teach use of NK-92 cells, while Santoli et al. teach in vivo use of cytotoxic cell lines. One of ordinary skill in the art would have been motivated to do so because Santoli et al. teach that lytic human derived cell lines can be used in vivo to treat disease or in preclinical in vivo studies (see column 10).

Office Action, ¶ 10.

20. The Examiner's statements are incorrect in view of the state of the tumor immunology art at the time that I invented the method of treating a pathology *in vivo* in a mammal by administering NK-92 cells, disclosed and claimed in the '955 Application. One skilled in the art would *not* have combined either Gong et al. with Santoli et al. at that time for at least the reasons set forth in paragraphs 21-40, *infra*.

21. Gong et al. disclosed the NK-92 cell line that I established from peripheral blood mononuclear cells of a fifty-year-old male patient who was diagnosed with an aggressive LGL lymphoma in 1992.

22. At the time that Gong et al. was written, I thought that the NK-92 cell line provided a suitable model to study the biology of NK-cells and activated NK-cells.

23. All experiments disclosed in Gong et al. were performed *in vitro*. Gong et al. partially characterized the cytotoxic profile of NK-92 cells.

24. The Examiner's characterization of Gong et al. is incorrect for at least the following reasons:

- a. The Examiner incorrectly states that "Gong et al. teach use of NK-92 cells to lyse leukemic tumor cells." See Office Action, ¶ 10. Rather, Gong et al. teach that NK-92 cells demonstrated cytotoxicity against two human leukemic cell lines, but do not teach that NK-92 cells are capable of lysing various tumor cells, including other leukemic tumor cells, of different origin or type.

COPY

c. While Gong et al. do not specifically teach that NK-92 cells are unacceptable for *in vivo* use, there is no teaching, suggestion, or motivation in Gong et al. that would lead one skilled in the art to use the NK-92 cell line *in vivo* to lyse tumor cells or as a cancer treatment, much less successfully reduce such a use to practice as a method of treating mammals. In fact, I did not initially recognize the importance or utility of the NK-92 cell line in a clinical setting.

25. Santoli et al. disclose genetically modified cytotoxic T lymphoblastic leukemia cell lines (T-ALL) 104, 107 and 103/2 and their use to treat cancer, both *in vivo* and *ex vivo*. The disclosure in Santoli et al. is limited to T-ALL cells. There is absolutely no teaching or suggestion in Santoli et al. with respect to cell lines in general, or with respect to NK-92 cells in particular, nor is their use described.

26. In fact, I was not aware of Santoli et al.'s T-ALL cell lines at the time that I created the unmodified NK-92 cell line (available from American Type Tissue Collection (ATCC) as Deposit No. CRL-2407) disclosed in Gong et al. or at the time that I arrived at the method of treating a pathology *in vivo* in a mammal by administering NK-92 cells disclosed in the '955 Application.

27. As one skilled in the art, it has been my experience that know-how with respect to one cell line cannot automatically be transferred or applied to another cell line, even where the cells are closely related, including with respect to culture conditions, requirements for growth factors such as IL-2, survival and signaling patterns following adoptive transfer, ability to migrate to tumor sites, sensitivity to chemotherapeutic agents, response to staining with vital dyes, ability to maintain their cytotoxic activity following

COPY

radiation, and susceptibility to gene transfer. Furthermore, the know-how required to use a specific cell line as a method of treatment cannot automatically be transferred or applied to another cell line and is dependent on the distinguishing characteristics of each cell line. Simply because one cell line has a specific utility does not mean that other closely related cell lines will have the same utility. Each must be proven independently and the specific conditions necessary for successful results, including treatment, determined.

28. In fact, as set forth below, the T-ALL cell line is not even comparable or related to the NK-92 cell line that I developed and disclosed in Gong et al. Accordingly, there was no reason apparent to one skilled in the art at the time I arrived at the claimed method of treating a pathology *in vivo* in a mammal by administering NK-92 cells to look to Santoli et al.'s teaching of T-ALL cells for any teaching with respect to methods of treatment with NK-92 cells.

a. The T-ALL cell lines were derived from a patient with ALL, whereas the NK-92 cell line was derived from a patient with an aggressive LGL lymphoma. These two diseases, leukemia and lymphoma, are in different disease categories and the cells derived therefrom are different cell lineages. As such, the cell lines each have unique characteristics in culture and in undergoing proliferation. One skilled in the art would therefore assume that these two cell lines are different and that conclusions with respect to one of the cell lines cannot be drawn to the other cell line.

COPY

b. T-ALL cells are of T-cell origin, are CD3-positive (a specific T-cell marker), CD8-positive, rearrange and express the T-cell receptor, are TCR $\alpha\beta$ -positive, and are characterized by specific chromosomal translocations. See Santoli et al., 1:68, 2:14, and 4:27. In addition, T-ALL cells lack natural cytotoxicity receptors such as NK-44 receptors that are found on NK-92 cells. In contrast, the NK-92 cell line is a true NK cell line (i.e., it is derived specifically from natural killer cells). NK-92 cells are CD3-negative, CD8-negative, do not express or rearrange the T-cell receptor complex (TCR), and have different chromosomal rearrangements than T-ALL cells. As such, one cannot infer the behaviors, transfectability, or cytotoxic mechanisms of NK-92 cells from those of T-ALL cells because the cells have different phenotypes.

c. NK-92 cells have unusual requirements for sub-culturing. Specifically, when cultured *in vitro* in α -minimum essential medium (α -MEM), the American Type Culture Collection (ATCC; Manassas, VA) recommends the media be supplemented with, among other things, 0.2 mM inositol, 0.1 mM 2-mercaptoethanol, 0.02 mM folic acid, 100-200 U/ml recombinant IL-2 (otherwise the cells die after 72 hours), and most surprisingly, a large proportion (25%) of two sera: 12.5% horse serum and 12.5% fetal bovine serum (FBS). In earlier passages, hydrocortisone is necessary. The cell density in culture is critical, and must be regularly checked and regulated by medium changes. The medium formulation, IL-2 concentration, serum concentration and cell density must be carefully regulated throughout the culture period. The culture of these cells is in

contrast to T-ALL cells, which require fetal bovine serum for growth and proliferation, and is similar to other well-established cell lines (or even hybridomas), such as Madin-Darby Canine Kidney (MDCK) cells, which can thrive in simple MEM with 5% (FBS) and 2mM L-glutamine, 10mM N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES), and sub-culturing once or twice a week.

d. Santoli et al. teach that T-ALL cells require antibody stimulation with CD2 or CD3 (a specific T cell marker) antigens to express (IFN)- γ , TNF- α , and GM-CSF. *See* Santoli et al. 2:18, 2:47. NK-92 cells do not require antibody stimulation to express (IFN)- γ , TNF- α , and GM-CSF, but rather release these cytokines in response to stimulation by IL-2.

e. Additionally, NK-92 cells are more stable than TALL-104 cells. Tam et al. (Hum. Gene Ther., 10: 1359-1373, 1999) have shown that NK-92 (both wild-type and transfected cells) cells require > 500 Gy to suppress proliferation, while Santoli et al. reported that TALL-104 cells require 40 Gy irradiation to suppress proliferation (*see* Santoli et al., Cancer Res., 56: 3021-3029, July 1996). Additionally, NK-92 cells maintain cytotoxicity and function even after irradiation, while T-ALL cells lose some cytotoxicity when irradiated.

f. Santoli et al. also reported that the standard treatment protocol for clinical trial in dogs required that the dogs be immunosuppressed using CsA, an immunosuppressive drug, starting the day before TALL-104 injections began and continuing through the first two weeks of TALL-104 injections. *See* Santoli et al.,

Cancer Res., 56: 3021-3029, July 1996). NK-92 cells do not require supplemental immunosuppression. These data suggest that TALL-104 cells are immunogenic while NK-92 cells are not.

29. Accordingly, given these significant phenotypic and functional differences between NK-92 cells and T-ALL cells, there was no reason apparent to one skilled in the art at the time I developed the method of treating a pathology *in vivo* in a mammal by administering NK-92 cells to look to Santoli et al.'s teaching of T-ALL cells to arrive at similar method of treatments. Because of the distinctive differences between these cell lines, the applicability and necessary requirements to use one of these cell lines as a method of treating *in vivo* is not applicable to the other, or any other cell line for that matter. The usefulness and necessary requirements for each would have to be characterized independently.

30. For at least the reasons set forth in paragraphs 21-29, *supra*, it would not have been obvious to one skilled in the art at the time the method of treating a pathology *in vivo* in a mammal by administering NK-92 cells was made to have combined the teachings of Gong et al. with Santoli et al. Most certainly one skilled in the art would not have had a reasonable expectation of success. If one skilled in the art were to have applied the teachings of Santoli et al to the NK-92 cells disclosed in Gong et al, they would not have had successful results because of the unique characteristics and requirements of these cells.

31. Additional comparative studies of NK-92 cells and TALL-104 cells further demonstrate that these cell lines are functionally quite different, with NK-92 cells having

significantly higher cytotoxic activity than TALL-104 cells. For example, many hematological cancers are susceptible to killing by NK-92 cells, whereas these cancers are mostly resistant to lysis by TALL-104 cells.

32. In fact, data disclosed in the '955 Application demonstrate that NK-92 cells are more cytolytic than TALL-104 or YT cells. See '955 Application, Tables 5 and 6, Fig. 9.

33. Notably, the results demonstrating that the NK-92 cell line is a superior cell line to the TALL-104 cell line were surprising.

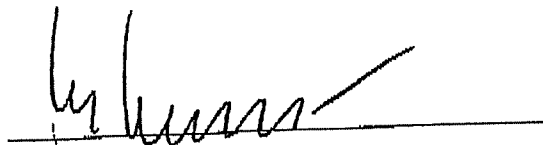
34. Given the significant phenotypic and functional differences between NK-92 cells and T-ALL cells and the cytotoxic superiority of NK-92 cells to TALL-104 cells, there was no reason apparent to one skilled in the art as of the filing date of the '955 Application to look to Santoli et al.'s teaching of TALL cells for treatment of disease for any teaching with respect to the NK-92 cells disclosed in Gong et al.

35. Neither of the references cited by the Examiner in the Final Office Action, either alone or in combination, teach or suggest the method of treatment with NK-92 cells disclosed and claimed in the '955 Application and therefore these references do not obviate the claimed method of treating a pathology *in vivo* in a mammal by administering NK-92 cells. In fact, we recently published in *Cytotherapy* (10(6): 625-632, 2008) Phase I trial results using NK-92 cells based on methods tailored to NK-92 cells, which are very different from methods tailored to TALL cells, and not disclosed or suggested in Santoli et al or Gong et al. See Exhibit 2 attached hereto. The results are promising and encourage continued development of the use of NK-92 cells as a method of treatment.

COPY

U.S. Patent Appn. Serial No. 10/008,955
Declaration of Hans Klingemann, M.D., Ph.D.
Filed in conjunction with Response to Final Office Action
filed on October 15, 2008

36. Signed at Boston, MA, this 15 day of
Oct., 2008.

A handwritten signature, likely of Hans Klingemann, is written over a horizontal line. The signature is in cursive and appears to be "H. Klingemann".

1391131_1.DOC

COPY

EXHIBIT 1

BIBLIOGRAPHY

I. Peer Reviewed Publications

1. **Klingemann H-G**, Brunswig D, Liehr H. Fibrinstruktur bei Hepatitis und Leberzirrhose. *Verh Dtsch Ges Inn Med* 1976; 82: 1649-1651.
2. **Klingemann H-G**, Brunswig D, Gunzer U. Störungen der Fibrin-polymerisation bei Paraproteinämien. *Verh Dtsch Ges Inn Med*. 1978; 84: 1356-1358.
3. **Klingemann H-G**, Brunswig D, Liehr H. Fibrinogen-und Fibrinstruktur bei Leberzirrhose. *Z Gastroenterol* 1978; 16: 564-573.
4. Verspohl F, Doss M, Tiepermann R, Schneider J, **Klingemann H-G**, Kaffarnik H. Einfluss von Formuladiaten auf den Porphyrinstoffwechsel bei akuter hepatischer Porphyrie. *Akt Ernährung* 1979; 6: 284-289.
5. **Klingemann H-G**, Egbring R, Havemann K. Structure of fibrin and fibrinmonomer in renal and hepatic failure. *Klin Wochenschr* 1980; 58: 533-535.
6. **Klingemann H-G**, Egbring R, Kaffarnik K. Effects of Polymyxin B and E on coagulation, thrombocyte function and fibrin structure. *Arzneimittelforschung* 1980; 30: 1719-1721.
7. **Klingemann H-G**, Schmidt U, Brunswig D, Egbring R, Kaffarnik H. Störungen der Blutgerinnung bei Leberzirrhose in Beziehung zum Ausmass der portalen Hypertension. *Fortschr Med* 1980; 98: 1561-1566.
8. Egbring R, Fuchs R, Beule J, **Klingemann H-G**. Anämien bei Blutungen infolge Störungen der Hämostase. *Therapiewoche* 1981; 31: 597-603.
9. **Klingemann H-G**, Egbring R, Havemann K. Verbrauchskoagulopathie. Pathogenese und Differentialtherapie. *Therapiewoche* 1981; 31: 3396-3398.
10. Egbring R, **Klingemann H-G**, Heimbürger N, Karges HE. Hyperfibrinolyse-Syndrom bei Paraproteinämie (IgG). *Med Welt* 1981; 31: 1427-1430.
11. **Klingemann H-G** & Egbring R. Heparin beim akuten Myokardinfarkt? *Dtsch Med Wochenschr* 1981;106: 479-483.
12. **Klingemann H-G**, Egbring R, Havemann K. Highly elevated factor XIII levels and defective fibrin formation in multiple myeloma. *Scand J Haematol* 1981;27: 253-26.
13. **Klingemann H-G**, Egbring R, Holst F, Gramse M, Havemann K. Digestion of Alpha₂-plasmin inhibitor by neutral proteases from human leukocytes. *Thromb Res* 1981; 24: 479-483.
14. **Klingemann H-G**, Sodomann CP, Kalbfleisch H, Havemann K. Follikuläre lymphatische Hyperplasie des Dünndarms bei Antikörpermangelsyndrom. *Dtsch Med Wochenschr* 1981; 106: 775-778.
15. Wehr M, Schmidt H, **Klingemann H-G**, Becker E, Hardewig A. Koronararterien-aneurysma: eine seltene Ursache der Angina pectoris. *Herz/Kreislauf* 1981;2: 137-141.

16. Klingemann H-G & Egbring R. Die Kumarinnekrose. *Med Welt* 1982; 33: 676-677.
17. Klingemann H-G & Egbring R. Platelet release proteins in patients with arterial occlusive disease on ticlopidine medication. *Dtsch Med Wochenschr* 1982; 107: 1388-1391.
18. Klingemann H-G, Egbring R, Holst F, Gramse M, Havemann K. Degradation of human plasma fibrin stabilizing factor XIII subunits by human granulocyte proteinases. *Thromb Res* 1982; 28: 793-801.
19. Klingemann H-G & Fibronectin - Klinische und biologische Aspekte. *Dtsch Med Wochenschr* 1982; 107: 1361-1365.
20. Broekmans AW, Bertina RM, Loeliger EA, Hofmann V, Klingemann H-G. Protein C and the development of skin necrosis during anticoagulant therapy. *Thromb Haemost* 1983; 49: 244.
21. Egbring R, Klingemann H-G, Gastpar H. Klinische Anwendungsmöglichkeiten für Heparin unter Ausschluss der thromboembolischen Erkrankungen. *Folia Angiologica* 1983; 30: 238-243.
22. Klingemann H-G, Kosukavak M, Hofeler H, Havemann K. Fibronectin and factor VIII R:AG in acute leukemia. *Hoppe Seylers Z Physiol Chem* 1983; 364: 269-277.
23. Klingemann H-G. Indikationen zum Einsatz von Heparin in der inneren Medizin. *Folia Angiologica* 1983; 30: 254-259.
24. Klingemann H-G. New clinical and biological aspects on factor XIII and fibronectin. *Blut* 1983; 46: 175-178.
25. Hofeler H & Klingemann H-G. Fibronectin and factor VIII-related antigen in liver cirrhosis and acute liver failure. *J Clin Chem Clin Biochem* 1984; 22: 15-19.
26. Klingemann H-G, Havemann K. Aplastische Anämie. *Dtsch Med Wochenschr* 1984; 109: 1816-1821.
27. Klingemann H-G & Broekmans AW, Bertina RM, Loeliger EA. Protein C deficiency - risk factor for venous thrombosis. *Klin Wochenschr* 1984; 62: 975-978.
28. Klingemann H-G, Hofeler H, Egbring R. Fibronectin - Plasmaprotein mit zahlreichen Aufgaben. *Dt Ärzteblatt* 1984; 81: 807-812.
29. Klingemann H-G & Storb R. Allogene Knochenmark-Transplantation. *Dt Ärzteblatt* 1985; 82: 1852-1861.
30. Klingemann H-G & Storb R. Cyclosporin in der allogenen Knochenmark-Transplantation. *Internist* 1985; 26: 569-574.
31. Klingemann H-G, Deeg HJ, Storb R. Knochenmark-Transplantation bei Chronisch Myeloischer Leukämie. *Dtsch Med Wochenschr* 1985; 110: 37-38.
32. Klingemann H-G. Chronisch Myeloische Leukämie. *Med Klin* 1985; 80: 24-32.
33. Klingemann H-G. Interactions in the formation of a fibrin clot. *Fortschr Med* 1985; 103: 276-278.
34. Seitz R, Lutz M, Michalik R, Lange H, Klingemann H-G, Egbring R. Fibronectin plasma levels after cadaver kidney transplantation. *Blut* 1985; 50: 35-43.
35. Klingemann H-G, Deeg HJ, Self S, Thomas ED, Storb R. Is race a risk factor for allogeneic marrow transplantation? *Bone Marrow Transplant* 1986; 1: 87-94.

COPY

36. Klingemann H-G, Ebert J, Deeg HJ. Fibronectin is present on B-cells but not on OKT 3-positive T-lymphocytes or Leu 11-positive natural killer cells. *J Leukoc Biol* 1986; 40: 491-495.
37. Klingemann H-G, Storb R, Fefer A, Deeg HJ, Appelbaum FR, Buckner CD, Cheever MA, Greenberg PD, Stewart PS, Sullivan KM, Witherspoon RP, Thomas ED. Bone marrow transplantation in patients aged 45 years and older. *Blood* 1986; 67: 770-776.
38. Klingemann H-G, Storb R, Sanders J, Deeg HJ, Appelbaum FR, Thomas ED. Acute lymphoblastic leukaemia after bone marrow transplantation for aplastic anaemia. *Br J Haematol* 1986; 63: 47-50.
39. Klingemann H-G, Tsoi M, Storb R. Fibronectin restores defective in vitro proliferation of lymphocytes of patients after marrow grafting. *Transplantation* 1986; 42: 412-417.
40. Klingemann H-G, Tsoi M, Storb R. Inhibition of prostaglandin E₂ restores defective lymphocyte proliferation and cell-mediated lympholysis in recipients after allogeneic marrow grafting. *Blood* 1986; 68: 102-107.
41. Klingemann H-G, Lum LG, Storb R. Phenotypical and functional studies on a subtype of suppressor cells (CD8+/CD11+) in patients after bone marrow transplantation. *Transplantation* 1987; 44: 381-386.
42. Klingemann H-G, Maunder RJ, Storb R. Reduced monocyte-associated fibronectin in patients after allogeneic marrow transplantation. *Transplantation* 1987; 43: 454-457.
43. Klingemann H-G, Self S, Banaji M, Deeg HJ, Doney K, Slichter SJ, Thomas ED, Storb R. Refractoriness to random platelet transfusions in patients with aplastic anemia: A multivariate analysis of data from 264 cases. *Br J Haematol* 1987; 66: 115-121.
44. Klingemann H-G, Tsoi M, Storb R. Fibronectin restores defective in vitro proliferation of lymphocytes from patients after marrow grafting. *Transplant Proc* 1987; 19: 2646-2647.
45. Klingemann H-G. Is there a place for the administration of immunoglobulins after bone marrow transplantation? *Klin Wochenschr* 1987; 65: 845-851.
46. Deeg HJ, Klingemann H-G. Bone marrow transplantation: Where do we stand? *Immunopath Immunother Forum* 1988; (Suppl. 2): 2-7.
47. Klingemann H-G, Eaves CJ. Colony stimulating factors. *Bone Marrow Transplant* 1988; 3: 177-184.
48. Klingemann H-G, Phillips GL. CMV immunoglobulin for prevention of pneumonitis after BMT. *Bone Marrow Transplant* 1988; 3: 235.
49. Shepherd JD, Shore TB, Reece DE, Barnett MJ, Klingemann HG, Buskard NA, Phillips GL. Cyclosporine and methylprednisolone for prophylaxis of acute graft-versus-host disease. *Bone Marrow Transplant* 1988; 3: 553-558.
50. Barnett MJ, Eaves CJ, Phillips GL, Kalousek DK, Klingemann H-G, Lansdorp PM, Reece DE, Shepherd JD, Shaw GJ, Eaves AC. Successful autografting in chronic myeloid leukaemia after maintenance of marrow in culture. *Bone Marrow Transplant* 1989; 4: 345-351.
51. Klingemann H-G, Dedhar S. Distribution of integrins on human peripheral blood mononuclear cells. *Blood* 1989; 74: 1348-1354.
52. Klingemann H-G, Deeg HJ. Granulocyte-macrophage colony-stimulating factor. *Drugs Future* 1989; 14: 243-247.

53. **Klingemann H-G.** Clinical application of recombinant human colony-stimulating factors. *Can Med Assoc J* 1989; 140: 137-142.
54. Phillips GL, Reece DE, Barnett MJ, Connors JM, Fay JW, Herzig GP, **Klingemann H-G**, Shepherd JD, Wolff SN. Allogeneic marrow transplantation for refractory Hodgkin's disease. *J Clin Oncol* 1989; 7: 1039-1045.
55. **Klingemann H-G**, Barnett MJ, Phillips GL. Use of an immunoglobulin preparation enriched for IgA to treat recurrent sinopulmonary infections in a patient with chronic GVHD. *Bone Marrow Transplant* 1990; 5: 205.
56. **Klingemann H-G**, Phillips GL. Double negative (CD4/CD8) T cell receptor a/b positive lymphocytes in patients with graft-versus-host disease. *Bone Marrow Transplant* 1990; 5: 364.
57. **Klingemann H-G**, Barnett MJ, Reece DE, Shepherd JD, Phillips GL. Use of an immunoglobulin preparation enriched for IgM (Pentaglobin) for the treatment of acute graft-versus-host disease. *Bone Marrow Transplant* 1990; 6: 199-202.
58. **Klingemann H-G**, Eaves AC, Barnett MJ, Reece DE, Shepherd JD, Belch AR, Brandwein JM, Langleben A, Koch PA, Phillips GL. Recombinant GM-CSF in patients with poor graft function after bone marrow transplantation. *Clin Invest Med* 1990; 13: 77-81.
59. **Klingemann H-G**, Eaves CJ, Phillips GL, Eaves AC. Hematopoietic growth factors as therapeutic agents: Their introduction in BC. *B C Med J* 1990; 32: 386-390.
60. Turhan AG, Humphries RK, Eaves CJ, Barnett MJ, Phillips GL, Kalousek DK, **Klingemann HG**, Lansdorp PM, Reece DE, Shepherd JD, Eaves AC. Detection of breakpoint cluster region-negative and nonclonal hematopoiesis in vitro and in vivo after transplantation of cells selected in cultures of chronic myeloid leukemia marrow. *Blood* 1990; 76: 2404-2410.
61. **Klingemann H-G**, Kohn FR. Involvement of fibronectin and its receptor in human lymphocyte proliferation. *J Leukoc Biol* 1991; 50: 464-470.
62. **Klingemann H-G**, Phillips GL. Immunotherapy after bone marrow transplantation. *Bone Marrow Transplant* 1991; 8: 73-81.
63. **Klingemann H-G**, Wong E. Interleukin-6 does not support interleukin-2 induced generation of human lymphokine-activated killer cells. *Cancer Immunol Immunother* 1991; 33: 395-397.
64. **Klingemann H-G**, Grigg AP, Wilkie-Boyd K, Barnett MJ, Eaves AC, Reece DE, Shepherd JD, Phillips GL. Treatment with recombinant interferon (α -2b) early after bone marrow transplantation in patients at high risk for relapse. *Blood* 1991; 78: 3306-3311.
65. **Klingemann H-G**, Kohn FR, Phillips GL. Proliferation of peripheral lymphocytes to interleukin-2 and interleukin-4 after marrow transplantation. *Eur Cytokine Netw* 1991; 2: 131-136.
66. **Klingemann H-G**, Storb R, Deeg HJ. Inhibition of cluster formation and lymphocyte proliferation by anti-fibronectin antiserum. *J Leukoc Biol* 1991; 49: 152-157.
67. Kohn FR, **Klingemann H-G**. Regulation of fibronectin receptor ($\alpha_5\beta_1$) gene expression in human monocytes and monocyte-derived macrophages by activation/differentiation signals. *Exp Hematol* 1991; 19: 653-658.
68. Kohn FR, Grigg ME, **Klingemann H-G**. Differential regulation of fibronectin receptor subunit gene and cell surface expression in human peripheral blood T lymphocytes. *J Immunol* 1991; 146: 1484-1489.

COPY

69. Kohn FR, Grigg ME, **Klingemann H-G**. Fibronectin receptor subunit (α_4 , α_5 and β_1) mRNA and cell surface expression in human peripheral blood B lymphocytes. *Immunol Lett* 1991; 28: 27-30.
70. Nevill TJ, Barnett MJ, **Klingemann H-G**, Reece DE, Shepherd JD, Phillips GL. Regimen-related toxicity of a busulfan-cyclophosphamide conditioning regimen in 70 patients undergoing allogeneic bone marrow transplantation. *J Clin Oncol* 1991; 9: 1224-1232.
71. Phillips GL, Barnett MJ, Brain MC, Chan K, Huebsch LB, **Klingemann H-G**, Meharchand J, Reece DE, Rybka WB, Shepherd JD, Spinelli JJ, Walker IR, Messner HA. Allogeneic bone marrow transplantation using unrelated donors: A pilot study of the Canadian Bone Marrow Transplant Group. *Bone Marrow Transplant* 1991; 8: 477-487.
72. Phillips GL, Reece DE, Shepherd JD, Barnett MJ, Brown RA, Frei-Lahr DA, **Klingemann H-G**, Boswell BJ, Spinelli JJ, Herzig RH, Herzig GP. High-dose cytarabine and daunorubicin induction and postremission chemotherapy for the treatment of acute myelogenous leukemia in adults. *Blood* 1991; 77: 1429-1435.
73. Phillips GL, Shepherd JD, Barnett MJ, Lansdorp PM, **Klingemann HG**, Spinelli JJ, Nevill TJ, Chan K-W, Reece DE. Busulfan, cyclophosphamide, and melphalan conditioning for autologous bone marrow transplantation in hematologic malignancy. *J Clin Oncol* 1991; 9: 1880-1888.
74. Reece DE, Barnett MJ, Connors JM, Fairey RN, Fay JW, Greer JP, Herzig GP, Herzig RH, **Klingemann H-G**, LeMaistre CF, O'Reilly SE, Shepherd JD, Spinelli JJ, Voss NJ, Wolff SN, Phillips GL. Intensive chemotherapy with cyclophosphamide, carmustine, and etoposide followed by autologous bone marrow transplantation for relapsed Hodgkin's disease. *J Clin Oncol* 1991; 9: 1871-1879.
75. Reece DE, Frei-Lahr DA, Shepherd JD, Dorovini-Zis K, Gascoyne RD, Graeb DA, Spinelli JJ, Barnett MJ, **Klingemann H-G**, Herzig GP, Phillips GL. Neurologic complications in allogeneic bone marrow transplant patients receiving cyclosporin. *Bone Marrow Transplant* 1991; 8: 393-401.
76. Shepherd JD, Pringle LE, Barnett MJ, **Klingemann H-G**, Reece DE, Phillips GL. Mesna versus hyperhydration for the prevention of cyclophosphamide-induced hemorrhagic cystitis in bone marrow transplantation. *J Clin Oncol* 1991; 9: 2016-2020.
77. **Klingemann H-G**, Shepherd JD, Eaves CJ, Eaves AC. The role of erythropoietin and other growth factors in transfusion medicine. *Transfus Med Rev* 1991; 5: 33-47.
78. Cuthbert RJG, Phillips GL, Barnett MJ, Nantel SH, Reece DE, Shepherd JD, **Klingemann H-G**. Anti-interleukin-2 receptor monoclonal antibody (BT 563) in the treatment of severe acute GVHD refractory to systemic corticosteroid therapy. *Bone Marrow Transplant* 1992; 10: 451-455.
79. **Klingemann H-G**. Trying to overcome residual disease after bone marrow transplantation for hematologic malignancies. *Leuk Lymphoma* 1992; 8: 421-429.
80. Kohn FR, Phillips GL, **Klingemann H-G**. Regulation of tumor necrosis factor- α production and gene expression in monocytes. *Bone Marrow Transplant* 1992; 9: 369-376.
81. Nevill TJ, Shepherd JD, Reece DE, Barnett MJ, Nantel SH, **Klingemann H-G**, Phillips GL. Treatment of myelodysplastic syndrome with busulfan-cyclophosphamide conditioning followed by allogeneic BMT. *Bone Marrow Transplant* 1992; 10: 445-450.
82. Nevill TJ, Tirgan MH, Deeg HJ, **Klingemann H-G**, Reece DE, Shepherd JD, Barnett MJ, Phillips GL. Influence of post-methotrexate folinic acid rescue on regimen-related toxicity and graft-versus-host disease after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1992; 9: 349-354.

COPY

83. Barnett MJ, Coppin CML, Murray N, Nevill TJ, Reece DE, **Klingemann H-G**, Shepherd JD, Nantel SH, Sutherland HJ, Phillips GL. High-dose chemotherapy and autologous bone marrow transplantation for patients with poor prognosis non-seminomatous germ cell tumours. *Br J Cancer* 1993; 68: 594-598.
84. **Klingemann H-G**, Deal H, Reid D, Eaves CJ. Design and validation of a clinically applicable culture procedure for the generation of interleukin-2 activated natural killer cells in human bone marrow autografts. *Exp Hematol* 1993; 21: 1263-1270.
85. **Klingemann H-G**, Neerunjun J, Schwulera U, Ziltener HJ. Culture of normal and leukemic bone marrow in interleukin-2: Analysis of cell activation, cell proliferation, and cytokine production. *Leukemia* 1993; 7: 1389-1393.
86. Reece DE, Barnett MJ, Connors JM, **Klingemann H-G**, O'Reilly SE, Shepherd JD, Sutherland HJ, Phillips GL. Treatment of multiple myeloma with intensive chemotherapy followed by autologous BMT using marrow purged with 4-hydroperoxycyclophosphamide. *Bone Marrow Transplant* 1993; 11: 139-146.
87. Reece DE, Elmongy MB, Barnett MJ, **Klingemann H-G**, Shepherd JD, Phillips GL. Chemotherapy with high-dose cytosine arabinoside and mitoxantrone for poor-prognosis myeloid leukemias. *Cancer Invest* 1993; 11: 509-516.
88. Shepherd JD, Barnett MJ, Connors JM, Spinelli JJ, Sutherland HJ, **Klingemann H-G**, Nantel SH, Reece DE, Currie CJ, Phillips GL. Allogeneic bone marrow transplantation for poor-prognosis non-Hodgkin's lymphoma. *Bone Marrow Transplant* 1993; 12: 591-596.
89. Shepherd JD, Reece DE, Barnett MJ, **Klingemann H-G**, Nantel SH, Sutherland HJ, Phillips GL. Induction therapy for acute myelogenous leukemia in patients over 60 years with intermediate-dose cytosine arabinoside, mitoxantrone and etoposide. *Leuk Lymphoma* 1993; 9: 211-215.
90. Toze CL, Barnett MJ, **Klingemann H-G**. Response of therapy-related myelodysplasia to low-dose interleukin-2. *Leukemia* 1993; 7: 463-465.
91. Barnett MJ, Eaves CJ, Phillips GL, Gascoyne RD, Hogge DE, Horsman DE, Humphries RK, **Klingemann H-G**, Lansdorp PM, Nantel SH, Reece DE, Shepherd JD, Spinelli JJ, Sutherland HJ, Eaves AC. Autografting with cultured marrow in chronic myeloid leukemia: Results of a pilot study. *Blood* 1994; 84: 724-732.
92. Brenner M, Krance R, Heslop HE, Santana V, Ihle J, Ribeiro R, Roberts WM, Mahmoud H, Boyett J, Moen RC, **Klingemann H-G**. Assessment of the efficacy of purging by using gene marked autologous marrow transplantation for children with AML in first complete remission. *Human Gene Therapy* 1994; 5: 481-499.
93. Cuthbert RJG, Shepherd JD, Nantel SH, Barnett MJ, Reece DE, **Klingemann H-G**, Chan KW, Spinelli JJ, Sutherland HJ, Phillips GL. Allogeneic bone marrow transplantation for severe aplastic anemia: The Vancouver experience. *Clin Invest Med* 1994; 18: 122-130.
94. Gong J, Maki G, **Klingemann H-G**. Characterization of a human cell line (NK-92) with phenotypical and functional characteristics of activated natural killer cells. *Leukemia* 1994; 8: 652-658.
95. **Klingemann H-G**, Eaves CJ, Barnett MJ, Eaves AC, Hogge DE, Nantel SH, Reece E, Shepherd JD, Sutherland HJ, Phillips GL. Transplantation of patients with high risk acute myeloid leukemia in first remission with autologous marrow cultured in interleukin-2 followed by interleukin-2 administration. *Bone Marrow Transplant* 1994; 14: 389-396.
96. **Klingemann H-G**, Gong H, Maki G, Horsman DE, Dalal BI, Phillips GL. Establishment and characterization of a human leukemic cell line (SR-91) with features suggestive of early hematopoietic progenitor cell origin. *Leuk Lymphoma* 1994; 12: 463-470.

COPY

97. **Klingemann H-G**, Wilkie-Boyd K, Rubin A, Onetto N, Nantel SH, Barnett MJ, Reece DE, Shepherd JD, Phillips GL. Granulocyte-macrophage colony-stimulating factor after autologous marrow transplantation for Hodgkin's disease. *Biotechnol Ther* 1994; 5: 1-13.
98. **Klingemann H-G**. Anti-IL-2 receptor antibody for prophylaxis and treatment of immunologic reactions after bone marrow and solid organ transplantation. *Drugs Future* 1994; 19: 659-663.
99. Kühr T, Dougherty GJ, **Klingemann H-G**. Transfer of the tumor necrosis factor α gene into hematopoietic progenitor cells as a model for site-specific cytokine delivery after marrow transplantation. *Blood* 1994; 84: 2966-2970.
100. Reece DE, Connors JM, Spinelli JJ, Barnett MJ, Fairey RN, **Klingemann H-G**, Nantel SH, O'Reilly S, Shepherd JD, Sutherland HJ, Voss N, Chan K, Phillips GL. Intensive therapy with cyclophosphamide, carmustine, etoposide \pm cisplatin, and autologous bone marrow transplantation for Hodgkin's disease in first relapse after combination chemotherapy. *Blood* 1994; 83: 1193-1199.
101. Fung H, Shepherd JD, Naiman SC, Barnett MJ, Reece DE, Horsman DE, Nantel SH, Sutherland HJ, Spinelli JJ, **Klingemann H-G**, Phillips GL. Acute monocytic leukemia: a single institution experience. *Leuk Lymphoma* 1995;19: 259-265.
102. **Klingemann H-G**, Phillips GL. Is there a place for immunotherapy with interleukin-2 to prevent relapse after autologous stem cell transplantation for acute leukemia? *Leuk Lymphoma* 1995;16: 397-405.
103. **Klingemann H-G**, Eaves CJ, Barnett MJ, Eaves AC, Hogge DE, Lansdorp P, Nantel SH, Reece DE, Shepherd JD, Sutherland HJ, Phillips GL. Autologous transplantation in patients with acute myeloid leukemia in first remission with IL-2-cultured marrow or peripheral blood stem cells followed by in vivo IL-2. *Onkologie* 1995; 18: 44-47.
104. **Klingemann H-G**. Introducing graft-versus-leukemia into autologous stem cell transplantation. *J Hematother* 1995; 4: 261-267.
105. Phillips GL, Nevill TJ, Spinelli JJ, Nantel SH, **Klingemann H-G**, Barnett MJ, Shepherd JD, Chan K, Meharchand JM, Sutherland HJ, Reece DE, Messner HA. Prophylaxis for acute graft-versus-host disease following unrelated-donor bone marrow transplantation. *Bone Marrow Transplant* 1995; 15: 213-219.
106. Przepiorka D, Weisdorf D, Martin P, **Klingemann H-G**, Beatty P, Hovs J, Thomas ED. Consensus conference on acute GVHD grading. *Bone Marrow Transplant* 1995; 15: 825-828.
107. Reece DE, Barnett MJ, Shepherd JD, Hogge DE, Klasa RJ, Nantel SH, Sutherland HJ, **Klingemann H-G**, Fairey RN, Voss NJ, Connors JM, O'Reilly SE, Phillips GL. High-dose cyclophosphamide, BCNU, and VP16-213 with or without cisplatin (CBV \pm P) and autologous transplantation for patients with Hodgkin's disease who fail to enter a complete remission after combination chemotherapy. *Blood* 1995; 86: 451-456.
108. Reece DE, Shepherd JD, **Klingemann H-G**, Sutherland HJ, Nantel SH, Barnett MJ, Spinelli JJ, Phillips GL. Treatment of myeloma using intensive therapy and allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1995;15: 117-123.
109. Tezcan H, Barnett MJ, Bredeson CN, Reece DE, Shepherd JD, Dalal BI, Horsman DE, **Klingemann H-G**, Nantel SH, Spinelli JJ, Sutherland HJ, Phillips GL. Treatment of acute promyelocytic leukemia in patients presenting at Vancouver General Hospital from 1983 to 1992. *Leuk Lymphoma* 1995;16: 439-444.

110. **Klingemann H-G**, Dougherty GJ. Site-specific delivery of cytokines in cancer. *Mol Medicine Today* 1996; 2: 154-159.
111. **Klingemann H-G**, Wong E, Maki G. A cytotoxic NK-cell line (NK-92) for ex vivo purging of leukemia from blood. *Biol Blood Marrow Transplant* 1996; 2: 68-75.
112. Wong EK, Eaves C, **Klingemann H-G**. Comparison of natural killer activity of human bone marrow and blood cells in cultures containing IL-2, IL-7 and IL-12. *Bone Marrow Transplant* 1996; 18: 63-71.
113. **Klingemann H-G**, Miyagawa B. Purging of malignant cells from blood after short ex vivo incubation with NK-92 cells. *Blood* 1996; 87: 4913-4914.
114. Miyagawa B, **Klingemann H-G**. Phagocytosis and burst activity of granulocytes and monocytes after stem cell transplantation. *J Lab Clin Med* 1997; 129: 634-637.
115. Dalal BI, Wu V, Barnett MJ, Horsman DE, Spinelli JJ, Naiman SC, Shepherd JD, Nantel SH, Reece DE, Sutherland HJ, **Klingemann H-G**, Phillips GL. Induction failure in de novo acute myelogenous leukemia is associated with expression of high levels of CD34 antigen by blasts. *Leuk Lymphoma* 1997; 3: 299.
116. Jackson SR, Tweeddale MG, Barnett MJ, Spinelli JJ, Sutherland HJ, Reece DE, **Klingemann H-G**, Nantel SH, Fung HC, Toze CL, Phillips GL, Sheperd JD. Admission of bone marrow transplant recipients to the intensive care unit: outcome, survival and prognostic factors. *Bone Marrow Transplant* 1998; 21: 697-704.
117. Simpson DR, Nevill TJ, Shepherd JD, Fung HC, Horseman DE, Nantel SH, Vickars LM, Sutherland HJ, Toze CL, Hogge DE, **Klingemann H-G**, Naiman SC, Barnett MJ. High incidence of extramedullary relapse of AML after busulfan/cyclophosphamide conditioning and allogeneic stem cell transplantation. *Bone Marrow Transplant* 1998; 22: 259-264.
118. Maki G, Takei F, **Klingemann H-G**. Induction of sensitivity to NK-mediated cytotoxicity by TNF- α treatment: Possible role of ICAM-3 and CD44. *Leukemia* 1998;12: 1565-72.
119. Yan Y, Steinherz P, **Klingemann H-G**, Denning D, Childs BH, McGuirk J, O'Reilly RJ. Antileukemia activity of a natural killer cell line against human leukemia. *Clin Cancer Res* 1998; 4: 2859-68.
120. Nevill TJ, Fung HC, Shepherd JD, Horseman DE, Nantel SH, **Klingemann H-G**, Forrest DL, Toze CL, Sutherland HJ, Hogge DE, Naiman SC, Lee A, Brockington DA, Barnett MJ. Cytogenetic abnormalities in primary myelodysplastic syndrome are highly predictive of outcome after allogeneic bone marrow transplantation. *Blood* 1998; 92: 1910-17.
121. Micallef INM, Chhanabhai M, Gascoyne RD, Shepherd JD, Fung HC, Nantel SH, Toze CL, **Klingemann H-G**, Sutherland HJ, Hogge DE, Neveill TJ, Lee A, Barnett MJ. Lymphoproliferative disorders following allogeneic bone marrow transplantation: the Vancouver experience. *Bone Marrow Transplant* 1998; 22: 981-987.
122. Reece DE, Nevill TJ, Sayegh A, Spinelli JJ, Brockington DA, Barnett MJ, **Klingemann H-G**, Connors JM, Nantel SH, Shepherd JD, Sutherland HJ, Voss NJ, Fairey RN, O'Reilly SE, Phillips GL. Regimen-related toxicity and non-relapse mortality with high-dose cyclophosphamide, carmustin (BCNU) and etoposide (VP16-213) (CBV) and CBV plus cisplatin (CBVP) followed by autologous stem cell transplantation. *Bone Marrow Transplant* 1999; 23: 1131-1138.
123. Tam YK, Miyagawa B, Ho VC, **Klingemann H-G**. Immunotherapy of malignant melanoma in a SCID mouse model using the highly cytotoxic natural killer cell line NK-92. *J Hematother* 1999; 8: 281-290.

124. Tam YK, Maki G, Miyagawa B, Hennemann B, Tonn T, **Klingemann H-G**. Characterization of genetically altered, interleukin 2 independent natural killer cell lines suitable for adoptive cellular immunotherapy. *Hum Gene Ther* 1999; 10: 1359 -1373.
125. Tam YK, & **Klingemann H-G**. Antileukemic effect of interleukin 2 transduced murine bone marrow after autologous transplantation. *Biol Blood and Marrow Transplant* 1999; 5: 231-242.
126. Hennemann B, Tam YT, Tonn T, **Klingemann H-G**. Expression of SCM-1 α /lymphotactin and SCM-1 β in natural killer cells is upregulated by IL-2 and IL-12. *DNA Cell Biol* 1999; 18: 565.
127. Lakhani A, Raptis A, Frame D, Simpson D, Berkahn L, Mellon-Reppen S, **Klingemann H-G**. Intravesicular instillation of ϵ -aminocaproic acid for patients with adenovirus-induced hemorrhagic cystitis. *Bone Marrow Transplant* 1999; 24: 1259 – 1260.
128. **Klingemann H-G**. Relevance and potential of natural killer cells in stem cell transplantation ? *Biol Blood Marrow Transplant*. 2000; 6: 90-99.
129. Toze CL, Shepherd JD, Connors JM, Voss NJ, Gascoyne RD, Hogge DE, **Klingemann H-G**, Nantel SH, Nevill TJ, Phillips GL, Reece DE, Sutherland HJ, Barnett MJ. Allogeneic bone marrow transplantation for low-grade lymphoma and chronic lymphocytic leukemia. *Bone Marrow Transplant* 2000; 25: 605 – 612.
130. McCaul KG, Nevill TJ, Barnett MJ, Toze CL, Currie CJ, Sutherland HJ, Conneally EA, Shepherd JD, Nantel DE, Hogge DE, **Klingemann H-G**. Treatment of steroid-resistant acute graft-versus-host disease with rabbit antithymocyte globulin. *J Hematol Stem Cell Res* 2000; 9: 367-374.
131. **Klingemann H-G**. Cellular therapy of cancer with natural killer cells: will it ever work ? *J Hematol Stem Cell Res* 2001; 10: 23 -26.
132. Reece, DE, Foon KA, Battacharya-Chatterjee M, Adkins D, Broun R, Connaghan DG, Dipertiso MD, Holland HK, Howard DS, Hale GA, **Klingemann H-G**, Munn RK, Raptis A, Phillips GL. Interim analysis of the use of anti-idiotypic breast cancer vaccine 11D10 (TriAb) in conjunction with autologous stem cell transplantation in patients with metastatic breast cancer. *Clin Breast Cancer* 2001; 2: 52-58.
133. Maki G, **Klingemann H-G**, Martinson JA, Tam YK. Factors regulating the cytotoxic activity of the human natural killer cell line, NK-92. *J Hematol Stem Cell Res* 2001; 10: 369-383.
134. Berkahn L, Simpson D, Raptis A, **Klingemann H-G**. In vivo purging with rituximab prior to collection of stem cells for autologous transplantation in chronic lymphocytic leukemia. *J Hematol Stem Cell Res* 2002, 11: 315.
135. Uherek C, Tonn T, Herrmann B, Becker S, Schnierle B, **Klingemann H-G**, Wels W. Retargeting of NK-cell cytolytic activity to ErbB2 expressing cancer cells results in efficient and selective tumor cell destruction. *Blood* 2002; 100: 1265 – 1273.
136. Reid GSD, Bharya S, **Klingemann H-G**, Schultz KR. Differential killing of pre-B acute lymphoblastic leukemia cells by activated NK cells and the NK-92ci cell line. *Clin Exp Immunol* 2002; 129: 265 – 271.
137. Tam, Y, Martinson JA, Doligosa K, **Klingemann H-G**. Ex vivo expansion of the highly cytotoxic human NK-92 cell line under cGMP conditions for clinical adoptive cellular immunotherapy. *Cytotherapy* 2003; 5: 259-272.
138. Maki G, Tam Y, Berkahn L, **Klingemann H-G**. Ex-vivo purging with NK-92 cells prior to autografting for chronic myelogenous leukemia. *Bone Marrow Transplant*. 2003; 31: 1119-25.

139. Klingemann H-G, Martinson J. Ex vivo expansion of natural killer cells for clinical application. *Cytotherapy*, 2004; 6:1, 15-22.
140. Zou G-M, Martinson JA, Tam Y, Klingemann H-G, The effect of LIGHT in inducing maturation of monocyte -derived dendritic cells from MDS patients. *Cancer Immunol Immunother* 53: 681 – 689, 2004
141. Kroeger N, Schilling G, Einsele H, Liebisch P, Shimoni A, Nagler A, Perez-Simon JA, San Miguel JF, Kiehl M, Fauser A, Schwerdtfeger R, Wandt H, Sayer HG, Myint H, Klingemann H-G, Zabelina T, Dierlamm J, Hinke A, Zander AR. Deletion of chromosome band 13q14 as detected by fluorescence in situ hybridization is a prognostic factor in patients with multiple myeloma receiving allogeneic dose-reduced stem cell transplantation. *Blood*, 103: 4056 – 4061, 2004
142. Kroeger N, Perez-Simon JA, Myint H, Klingemann H-G, Shimoni A, Nagler A, Martino R, Allegre A, Tomas JF, Schwerdtfeger R, Kiehl M, Fauser A, Sayer HG, Leon A, Beyer J, Zabelina T, Ayuk F, San Miguel JF, Brand R Zander AR. Relapse to prior autograft and chronic GvHD are the strongest prognostic factors for outcome of melphalan/fludarabine based dose-reduced allogeneic stem cell transplantation in patients with multiple myeloma. *Biol Blood Marrow Transplant* 10: 698 – 708, 2004
143. Miller CB, Waller EK, Klingemann H-G, Dignani MC, Anaissie EJ, Cagnoni PJ, McSweeney P, Fleck PR, Fruchtman SM, McGuirk J, Chao NJ. Lipid formulations of amphotericin B preserve and stabilize renal function in HSCT recipients. *Bone Marrow Transplant* 33: 543 – 548, 2004
144. Bae J, Martinson J, Klingemann H-G. Identification of novel CD33 antigen specific peptides for the generation of cytotoxic T-lymphocytes against acute myeloid leukemia. *Cell Immunol* 227: 38-50, 2004
145. Martinson JA, Bae J, Klingemann H-G, Tam YK Activated platelets rapidly up-regulate CD40L expression and can effectively mature and activate autologous, ex vivo differentiated dendritic cells. *Cytotherapy*, 6: 487-497, 2004
146. Bae J, Martinson JA, Klingemann H-G. Heteroclitic CD33 peptides with enhanced anti - acute myeloid leukemic immunogenicity. *Clin Cancer Res* 10:, 7043 – 52, 2004
147. Bae J, Martinson JA, Klingemann H-G. Identification of CD19 and CD20 peptides for induction of antigen-specific lymphocytes against B-cell malignancies. *Clin Cancer Res* 11: 1629-1638, 2005
148. Rondelli D, Barosi, G, Bacigalupo A, Prchal JT, Alessandrino EP, Spivak JL, Smith BD, Klingemann H-G, Fruchtman S, Hoffman R. Allogeneic hematopoietic stem cell transplantation with reduced -intensity conditioning in intermediate -or high-risk patients with myelofibrosis with myeloid metaplasia. *Blood* 105: 4115 – 4119, 2005
149. Xiulong X, Rao G, Gaffud MJ, Ding HG, Maki G, Klingemann H-G, Groh V, Spies T, Caillat-Zucman S, Gattuso P, Plate J, Prinz RA. Clinicopathological significance of major histocompatibility complex class I related chain A and B (MICAA/B) expression in thyroid cancer. *J Clin Endocrinol Metabol* 91:2704-12, 2006
150. Klingemann H, Rainov NG, Smythe JA , Tuitou E. Editorial Board Focus 2007. *Expert Opin Biol Ther* 7: 573-5: 2007
151. Mueller T, Uhrek C, Maki G, Chow KU, Schimpf A. Klingemann H-G, Tonn T, Wels WS. Expression of a CD20-specific antigen receptor enhances activity of NK cells and overcomes NK-resistance of lymphoma and leukemia cells. *Cancer Immunol Immunother*, DOI 10.1007/s00262-007-0383-3

152. Friedman R., Betancur M, Tuncer H, Boissel L. **Klingemann, H.** Umbilical cord mesenchymal stem cells: adjuvants for human cell transplantation, *Biol Blood Marrow Transplant*, 2007; 13: 1477-1486
153. **Klingemann H**, Boissel, L. Targeted cellular therapy with natural killer cells. *Horm Metab Res*. 2008; 40: 122-125

Review Papers/Editorials

1. **Klingemann H-G.** Mechanical ventilation for bone marrow transplant patients: when does it become futile (Editorial) *Critical Care Med* 2000; 28: 899 – 900.
2. **Klingemann H-G.** Immunotherapy with dendritic cells: coming of age ? (Editorial) *J Hematoth Stem Cell Res* 2000; 9: 127-128.
3. **Klingemann H-G.,** Schumer M, Friend P. Evolving infrastructural issues in blood and marrow transplant center development. *Graft* 2001; 4: 418 – 420.
4. D. English & **Klingemann H-G.** The foundation of cellular therapy: Barnes and Loutit, 1957 (Editorial) *J Hematoth Stem Cell Res* 2001 ; 10: 323-324.
5. **Klingemann H -G.** Cellular Therapy: Finishing the job. (Editorial) *J Hematoth Stem Cell Res* 2001; 10: 435-436.
6. **Klingemann H-G.** STI – Stop Transplanting Immediately ? (Editorial) *J Hematoth Stem Cell Res* 2002; 11: 165-167.
7. Meagher RC, **Klingemann H-G.** Human umbilical cord blood cells: how useful are they for the clinician ? *J Hematoth Stem Cell Res* 2002; 11: 445 – 448.
8. **Klingemann H-G.** Mini-Transplants turning micro: how low can we go ? *J Hematoth Stem Cell Res* 2002; 11: 859 – 862.
9. Arai S, **Klingemann H-G.** Stem cell transplantation for myelodysplasia. *Cancer Treat Res* 2001; 108:159-68.
10. Arai S, **Klingemann H-G.** Hematopoietic stem cell transplantation: bone marrow versus mobilized peripheral blood. *Arch Med Res* 2003; 34: 454-553.
11. Arai S, **Klingemann H-G.** Role of immunotherapy in stem cell transplantation. *Int J Hematol* 77: 22 – 28, 2003
12. **Klingemann H-G.** Natural killer cell based immunotherapeutic approaches. *Cytotherapy* 7: 16-22, 2005
13. Arai S, **Klingemann H-G.** Natural killer cells: can they be useful as adoptive immunotherapy for cancer ? *Expert Opin Biol Ther* 5: 163-72, 2005

III. Non-Peer Reviewed Publications/Conference Proceedings

1. Phillips GL, Barnett MJ, **Klingemann H-G**. Status of autologous bone marrow transplantation in Canada. Terry Fox Cancer Research Workshop on Autologous Bone Marrow Transplantation. *Ann R Coll Phys Surg Can* 1990; 223: 57-58..
2. Barnett MJ, Sutherland HJ, Eaves AC, Hogge DE, Humphries RK, **Klingemann H-G**, Lansdorp PM, Phillips GL, Reece DE, Shepherd JD, Eaves CJ. Human hematopoietic stem cells in long-term culture: Quantitation and manipulation. *Bone Marrow Transplant* 1991; 7 (Suppl. 1): 70.
3. Barnett MJ, Eaves CJ, Phillips GL, Hogge DE, Humphries RK, **Klingemann H-G**, Lansdorp PM, Reece DE, Shepherd JD, Eaves AC. Autografting with curative intent for patients with chronic myeloid leukemia. In: *Autologous Bone Marrow Transplantation, Proceedings of the Fifth International Symposium*. (eds. KA Dicke, JO Armitage, MJ Dicke-Evinger), The University of Nebraska Medical Center, Omaha, 1991; pp. 237-240.
4. Phillips GL, Barnett MJ, Bolwell BJ, Brown RA, Connors JM, Fay JW, Harden EA, Herzig GP, Herzig RH, Lansdorp PM, **Klingemann H-G**, Meagher RC, Murphy CP, Reece DE, Shepherd JD, Stevens DA, Wolff SN. Augmented CBV regimens and autologous bone marrow transplantation in Hodgkin's disease. In: *Autologous Bone Marrow Transplantation, Proceedings of the Fifth International Symposium*. (eds. KA Dicke, JO Armitage, MJ Dicke-Evinger), The University of Nebraska Medical Center, Omaha, 1991; pp. 501-508.
5. Barnett MJ, Eaves CJ, Phillips GL, Hogge DE, **Klingemann H-G**, Lansdorp PM, Nantel SH, Reece DE, Shepherd JD, Sutherland HJ, Eaves AC. Autografting in chronic myeloid leukemia with cultured marrow. *Leukemia* 1992; 6 (Suppl. 4): 118-119.
6. **Klingemann H-G**, Deal H, Reid D, Eaves CJ. Preclinical evaluation of a bone marrow autograft culture procedure for generating lymphokine-activated killer cells in vitro. *Can J Infect Dis* 1992; 3 (Suppl. B): 123B-127B.
7. Barnett MJ, Eaves CJ, Phillips GL, Hogge DE, **Klingemann H-G**, Lansdorp PM, Nantel SH, Reece DE, Sutherland HJ, Eaves AC. Autografting in chronic myeloid leukemia with cultured marrow: Results of a pilot study. In: *Autologous Bone Marrow Transplantation, Proceedings of the Sixth International Symposium*. (eds. KA Dicke, A Keating, NC Gorin, C Nichols, A Yeager), Cancer Treatment Research Education Fund, Arlington, Texas, 1993; pp. 209-211.
8. **Klingemann H-G**, Blaise D. New directions -- immunotherapy and autologous stem cell transplantation. *Bone Marrow Transplant* 1993; 12 (Suppl. 4): 136-137.
9. Barnett MJ, Eaves CJ, Phillips GL, Hogge DE, **Klingemann H-G**, Lansdorp PM, Nantel SH, Reece DE, Shepherd JD, Sutherland HJ, Eaves AC. Autografting in chronic myeloid leukemia with cultured marrow: Update of the Vancouver study. *Stem Cells* 1993; 11 (Suppl. 3): 64-66.
10. **Klingemann H-G**, Shepherd JD, Reece DE, Barnett MJ, Nantel SH, Sutherland HJ, Spinelli JJ, Phillips GL. Regimen-related acute toxicities: Pathophysiology, risk factors, clinical evaluation and preventive strategies. *Bone Marrow Transplant* 1994; 14 (Suppl. 4): S14-S18.

COPY

11. Barnett MJ, Eaves CJ, Phillips GL, Gascoyne RD, Hogge DE, Horsman DE, Humphries RK, **Klingemann H-G**, Lansdorp PM, Nantel SH, Reece DE, Shepherd JD, Spinelli JJ, Sutherland HJ, Eaves AC. Autografting in chronic myeloid leukemia with cultured marrow: update of the Vancouver pilot study. In: *Autologous Marrow and Blood Transplantation. Proceedings of the Seventh International Symposium*, (eds. KA Dicke, A Keating), The Cancer Treatment Research and Educational Institute, Arlington, Texas, 1995; pp. 477-480.
12. **Klingemann H-G**, Eaves CJ, Barnett MJ, Eaves AC, Hogge DE, Lansdorp P, Nantel SH, Reece DE, Shepherd JD, Sutherland HJ, Phillips GL. Autologous transplantation in patients with acute myeloid leukemia in first remission with IL-2 cultured marrow or peripheral blood stem cells followed by *in vivo* IL-2. In: *Autologous Marrow and Blood Transplantation. Proceedings of the Seventh International Symposium*, (eds. KA Dicke, A Keating), The Cancer Treatment Research and Educational Institute, Arlington, Texas, 1995; pp. 95-102.
13. **Klingemann H**. Role of postinduction immunotherapy in acute myeloid leukemia. *Leukemia* 1996; 10 : S21-S22.
14. **Klingemann H-G**. Ex vivo treatment of autologous grafts with IL-2 prior to transplanttaion in patients with AML in first remission. In: *Autologous Marrow and Blood Transplantation. Proceedings of the Seventh International Symposium*, (eds. KA Dicke, A Keating), The Cancer Treatment Research and Educational Institute, Arlington, Texas, 1997; pp. 619-623.
15. **Klingemann H-G**, Berkahn L, Raptis A, Simpson D, Tam Y. Antitumor Immunotherapy in autologous transplantation. In: *Autologous Blood and Marrow Transplantation. Proceedings of the Ninth International Symposium*, (eds. KA Dicke, A Keating), The Cancer Treatment Research and Educational Institute, Arlington, Texas, 1999; pp. 661-664.
16. **Klingemann H-G**. Strategies in autologous transplantation. In: *Autologous Blood and Marrow Transplantation. Proceedings of the Ninth International Symposium*, (eds. KA Dicke, A Keating), The Cancer Treatment Research and Educational Institute, Arlington, Texas, 1999; pp. 735-736.
17. Toze CL, Shepherd JD, Connors JM, Voss NJ, Gascoyne RD, Hogge DE, **Klingemann H-G**, Nantel SH, Nevill TJ, Phillips GL, Reece DE, Sutherland HJ, Barnett MJ. Allografting for indolent lymphoid neoplasms. *Annals of Oncology* (Suppl 1): 2000 ; S 59 - S 61.
18. Reece, DE, Foon KA, Chatterjee M, Adkins D, Broun R, Connaghan DG, Diperiso MD, Holland HK, Howard DS, Hale GA, **Klingemann H-G**, Munn RK, Raptis A, Phillips GL. Use of the Anti-idiotype Breast Cancer Vaccine 11D10 in Conjunction with Autologous Stem Cell Transplantation in Patients with Metastatic Breast Cancer. *Clin Breast Cancer* 2003; Suppl 4:S152-7
154. Uherek C, Mueller T, Tonn T, Uherek B, **Klingemann H-G**, Wells WS. Genetically modified natural killer cells specifically recognizing the tumor -associated antigens ErbB2/HER2 and EpCAM. *Cancer Cell Intern* 4 (Suppl 1): S 7, 2004

III. BOOKS (Authored)/ Special Journal Issues (Editor)

1. Guest Editor. *Factor XIII and fibronectin - New clinical and biological approaches*. Medizinische Verlagsgesellschaft, Marburg, 1983.
2. Deeg HJ, **Klingemann H-G**, Phillips GL. *A Guide to Bone Marrow Transplantation*. Springer Verlag, Berlin, 1988.
3. Deeg HJ, **Klingemann H-G**, Phillips GL. *A Guide to Bone Marrow Transplantation*. 1st Japanes Edition, Springer Verlag, Berlin, 1990.

4. Deeg HJ, **Klingemann H-G**, Phillips GL. *A Guide to Bone Marrow Transplantation*. 2nd Edition, Springer Verlag, Berlin, 1992.
5. Deeg HJ, **Klingemann H-G**, Phillips GL. Van Zant G. *A Guide to Blood and Marrow Transplantation*. 3rd Edition, Springer Verlag, Berlin, 1998.
6. Deeg HJ, **Klingemann H-G**, Phillips GL. Van Zant G. *A Guide to Blood and Marrow Transplantation*. 2nd Japanes Edition, Springer Verlag, Berlin, 1999.
7. Deeg HJ, **Klingemann H-G**, Phillips GL. Van Zant G. *A Guide to Blood and Marrow Transplantation*. 3rd Japanes Edition, Springer Verlag, Berlin, 2000.
8. **Klingemann H-G**. Graft Versus Host Disease. Guest Editor of a Special Focus Issue. *J Hematoth Stem Cell Res*. 9 (3): 2000.
9. **Klingemann H-G**. Cellular Therapies. Guest Editor of a Special Focus Issue. *J Hematoth Stem Cell Res* 10 (4): 2001.

Book Chapters

1. Egbring R, Menche CH, Jacoby S, **Klingemann H-G**, Hofmann A, Fuchs A, Heimburger N, Havemann K. Vergleichende Antithrombin III Bestimmung bei Patienten mit akuten Leukamien, Septikamien, chronischen Lebererkrankungen, Malignomen und Thrombosen sowie vor und nach Antithrombin I. *Fibrinolyse, Thrombose, Haemostase* (eds. E Deutsch, K Lechler), Schattauer Verlag, Stuttgart, 1980; pp 550-553.
2. **Klingemann H-G**, Heuser E, Hein J, Kaffarnik H. Endoskopische Diagnostik einer follikularen Lymphatischen Hyperplasies des Terminalen Ileum. *Fortschritte der Gastroenterologischen Endoskopie* (ed. H Henning), G. Witzstrock Verlag, Baden-Baden, Koln, New York, 1980; pp 120-123.
3. Egbring R, **Klingemann H-G**, Holst F, Gramse M, Havemann K. Proteolyse von Plasmininhibitor, Faktor XIII-Untereinheiten und Fibronectin durch Granulozytenenzyme. *Hamostase, Thrombophilie und Arteriosklerose* (eds. J van de Loo, R Asbeck), Schattauer Verlag, Stuttgart, 1982; pp 739-743.
4. Egbring R, **Klingemann H-G**, Seitz R, Heimburger N, Karges HE, Havemann K. Erfahrungen mit der Antithrombin III Substitution bei Patienten mit akutem Leversversagen nach Tetrachlorkohlenstoff-Vergiftung. *Hamostase, Thrombophilie und Arteriosklerose*, (eds. J van de Loo, F Asbeck), Schattauer Verlag, Stuttgart, 1982; pp 642-647.
5. **Klingemann H-G**, Egbring R, Havemann K. Einfluss von Tiklopidin auf erhoehte Plasmakonzentrationen von b-TG und PF 4 bei arterieller Verschlusskrankheit. *Hamostase, Thrombophilie und Arteriosklerose*, (eds. J van de Loo, R Asbeck), Schattauer, Verlag, Stuttgart, 1982; pp 69-73.
6. **Klingemann H-G**. Kongenitale Dysfibrinogenamie. Atlas der Resonanzthrombographie, (ed. E Hiller), Hygieneplan, 1982.
7. Egbring R, **Klingemann H-G**, Arke K, Karges HE. Alpha₂-antiplasmin-plasmin complexes in patients with hyperfibrinolysis. Progress in Fibrinolysis VI, (eds. JF Davidson, F Bachmann, CA Bouvier, EKO Kruithof), Churchill Livingstone, 1983; pp 397-401.

COPY

8. Egbring R, **Klingemann H-G**, Gramse M, Havemann K. Factor XIII deficiency in patients with septicemia. Factor XIII and Fibronectin, (eds. R Egbring, H Klingemann), Medizinische Verlagsgesellschaft, Marburg 1983; pp 91-105.
9. **Klingemann H-G**, Krause T, Egbring R. Factor XIII activity in thrombocytopenic patients. Factor XIII and Fibronectin, (eds. R Egbring, H Klingemann), Medizinische Verlagsgesellschaft, Marburg, 1983; pp 163-165.
10. **Klingemann H-G**. Use of granulocyte-macrophage colony stimulating factor (GM-CSF) to support intensive chemotherapy. Effects of Therapy on Biology and Kinetics of the Residual Tumor, Part B: Clinical Aspects, (eds. J Ragaz, L Simpson-Herrin, ME Lippman, B Fisher), Wiley-Liss, New York, 1990; pp 211-218.
11. **Klingemann H-G**, Gong H, Eaves CJ, Phillips GL. Immunotherapy in marrow transplantation - interferon early after transplantation or IL-2 activated bone marrow. Cytokines in Cancer Therapy, Vol. 46, (eds. L Bergmann, PS Mitrou), Basel, Karger, 1994; pp 168-174.
12. **Klingemann H-G**, Barnett MJ, Kuhr T. Interferons as immunotherapeutic agents after marrow transplantation. Immunotherapy and Bone Marrow Transplantation, (eds. T Spitzer, A Mazumder), Futura Publishing Co. Armonk, New York, 1995; pp 121-136.
13. Barnett MJ, **Klingemann H-G**, Eaves CJ, Eaves AC. Autografting with cultured marrow for the myeloid leukemias: the Vancouver experience. Autologous Stem Cell Transplantations: Biological and Clinical Results in Malignancies, (ed. AM Carella), Harwood Academic Publishers, (in press)
14. H.- G. Klingemann. Biologic therapy after hematopoietic stem cell transplantation. In: Hematopoietic stem cell therapy. Eds: Ball, EE, Lister J, Law P. Churchill Livingstone, New York, Edinburgh, London, Philadelphia, 2000; pp 660 – 667.
15. H-G Klingemann & HJ Deeg. Stem cell transplantation for myelodysplasia. In: Myelodysplastic syndromes and secondary acute myelogenous leukemia. Eds: A. Raza & S Mundle. Kluwer Academic Publishers, 2001; pp 159-168.

IV. ABSTRACTS (Published)

1. Brunswig D, **Klingemann H-G**, Liehr H. Incomplete fibrin formation in liver cirrhosis. Digestion 1975; 12: 260,
2. **Klingemann H-G**, Egbring R, Kaffarnik H. Changes in fibrin monomer and fibrinstructure in patients with renal failure. Thromb Haemost 1979; 42: 445.
3. Egbring R, **Klingemann H-G**, Heimbürger N, Karges HE. Hyperfibrinolysis in a patient with IgG-paraproteinaemia. Thromb Haemost 1981; 46: 389.
4. Egbring R, **Klingemann H-G**, Heimbürger N, Karges HE, Beule J, Seitz R, Havemann K. Antithrombin III substitution in acute hepatic failure due to CCl₄ intoxication. Thromb Haemost 1981; 46: 50.
5. Holst F, **Klingemann H-G**, Egbring R, Bohn H, Havemann K. Effect of leucocyte proteases on structure and activity of isolated factor XIII subunit A and S. Thromb Haemost 1981; 46: 241.

COPY

6. **Klingemann H-G**, Egbring R, Havemann H. β -thromboglobulin and HA-platelet factor 4 in multiple myeloma, Hodgkin's disease and malignant lymphoma - effects of therapy. *Thromb Haemost* 1981; 6: 430.
7. **Klingemann H-G**, Egbring R, Karges HE. Hyperfibrinolysis bei Leberzirrhose und akutem Leberversagen. *Z Gastroenterol* 1982; 20: 570.
8. **Klingemann H-G**, Egbring R, Gramse M, Havemann K. Effects of leukocytic proteinases on fibronectin, α_2 -plasmin inhibitor and factor XIII subunits. *Blut* 1982; 45: 185.
9. **Klingemann H-G**, Hofeler H, Havemann K. Fibronectin in acute leukemia. *Blut* 1982; 45: 206.
10. **Klingemann H-G**, Hofeler H, Lorenz-Meyer H. Fibronectin im Plasma bei Leberzirrhose und akutem Leberversagen. *Z Gastroenterol* 1982; 20: 519.
11. Egbring R, Liesenfeld A, Seitz R, **Klingemann H-G**. Antithrombin III and plasma derivative (PPSB and fresh frozen plasma) substitution in patients with acute liver failure. *Thromb Haemost* 1983; 50: 442.
12. **Klingemann H-G**, Kosukavak M, Hofeler H. Fibronectin-fibrinogen crosslinking as diagnostic tool? *Thromb Haemost* 1983; 50: 399.
13. Kosukavak M, **Klingemann H-G**. A rapid latex assay for determination of plasma fibronectin. *Thromb Haemost* 1983; 50: 245.
14. Seitz R, Lutz H, Michalik R, **Klingemann H-G**. Fibronectin after renal transplantation. *Thromb Haemost* 1983; 50: 440.
15. **Klingemann H-G**, Storb R, Fefer A, Deeg HJ, Thomas ED. Bone marrow transplantation in patients 45 years and older. *Blut* 1985; 51: 159.
16. **Klingemann H-G**, Tsoi M, Thomas ED, Storb R. Prostaglandin E2 restores defective in vitro lymphocyte function after bone marrow transplantation. *Blood* 1985; 66 (Suppl. 1): 260a.
17. **Klingemann H-G**, Ebert J, Storb R, Deeg HJ. Cluster formation and proliferation of canine lymphocytes is inhibited by antifibronectin antiserum. *J Leukoc Biol* 1986; 40: 311.
18. **Klingemann H-G**, Self S, Banaji M, Deeg HJ, Doney K, Slichter SJ, Thomas ED, Storb R. Multivariate analysis of refractoriness to random platelets in 264 patients with aplastic anemia who presented for marrow transplantation. *Blood* 1986; 68 (Suppl. 1): 299a.
19. **Klingemann H-G**, Lum LG. Different CD8 positive suppressor cell subtypes in patients after bone marrow transplantation. *J Leukoc Biol* 1987; 42: 330.
20. **Klingemann H-G**, Phillips GL, Eaves AC. Subtypes of suppressor cells in patients after bone marrow transplantation. *Clin Invest Med* 1987; 10: B84.
21. Shepherd JD, Reece DE, Shore T, Barnett MJ, **Klingemann H-G**, Phillips GL. Cyclosporine/methylprednisolone prophylaxis for acute graft-vs-host disease. *Clin Invest Med* 1987; 10 (Suppl. B): 80.
22. Barnett MJ, Eaves CJ, Phillips GL, Kalousek DK, **Klingemann H-G**, Lansdorp PM, Reece DE, Shaw GJ, Eaves AC. Treatment of chronic myeloid leukemia with intensive therapy supported by transplantation of autologous bone marrow maintained in long-term culture. *Clin Res* 1988; 36: 406A.

23. Barnett MJ, Eaves CJ, Phillips GL, Kalousek DK, **Klingemann H-G**, Lansdorp PM, Reece DE, Shaw GJ, Eaves AC. Rapid reconstitution of Philadelphia chromosome-negative hematopoiesis in patients with chronic myeloid leukemia transplanted with cultured autologous bone marrow to support intensive therapy. *Blood* 1988; 72 (Suppl. 1): 379a.
24. **Klingemann H-G**, Dedhar S, Kohn FR, Phillips GL. Fibronectin increases lymphocyte proliferation by mediating adhesion between immunoreactive cells. *J Cell Biochem* 1988; (Suppl. 12E): 174.
25. **Klingemann H-G**, Dedhar S, Phillips GL, Eaves A. Receptors for fibronectin and vitronectin on blood mononuclear cells of normals and marrow transplant recipients. *Clin Invest Med* 1988; 11: C55.
26. Phillips G, Barnett M, Buskard N, Connors J, Fay J, Herzig G, Herzig R, Klimo P, **Klingemann H-G**, LeMaistre F, Lowder J, Moquin J, O'Reilly S, Reece D, Wolff S, Voss N. Augmented cyclophosphamide (C), BCNU (B) and etoposide (V) = CBV and autologous bone marrow transplantation (BMT) for progressive Hodgkin's disease (HD). *J Cell Biochem* 1988; (Suppl. 12C): 122.
27. Reece D, Barnett M, Connors J, Fay J, Herzig G, Herzig R, Klimo P, **Klingemann H-G**, LeMaistre F, Lowder J, Moquin JP, O'Reilly S, Wolff S, Voss N, Phillips G. Augmented cyclophosphamide (C), BCNU (B), and etoposide (V) = CBV and autologous bone marrow transplantation (BMT) for progressive Hodgkin's disease (HD). 1988; *Blood* 72 (Suppl. 1): 402a.
28. Shepherd JD, Reece DE, Phillips GL, Barnett MJ, Buskard NA, Herzig RH, **Klingemann H-G**, Herzig GP. High dose cytosine arabinoside (HDARA-C) and daunorubicin (DNR) as initial induction and consolidation therapy in acute myelogenous leukemia. 1988; *Blood* 72 (Suppl. 1): 226a.
29. Turhan AG, Eaves CJ, Humphries RK, Barnett MJ, Phillips GL, **Klingemann HG**, Reece DE, Shepherd JD, Kalousek DK, Eaves AC. Polyclonal and BCR-negative hemopoiesis in vivo after transplantation of autologous CML marrow cultured under conditions that eliminate BCR-positive cells. *Blood* 1988; 72 (Suppl. 1): 184a.
30. Reece D, Barnett M, Connors J, **Klingemann H-G**, O'Reilly S, Fairey R, Shepherd J, Voss N, Phillips G. Intensive cyclophosphamide (C), BCNU (B), etoposide (V) plus cisplatin (P) = CBVP and autologous bone marrow transplantation (BMT) for progressive Hodgkin's disease (HD). *Clin Invest Med* 1989; 12 (Suppl. B): 46.
31. Reece DE, Barnett MJ, Connors JM, **Klingemann H-G**, O'Reilly SE, Shepherd JD, Phillips GL. Intensive therapy with busulfan, cyclophosphamide and melphalan (BUCY + MEL) and 4-hydroperoxycyclophosphamide (4-HC) purged autologous bone marrow transplantation (AutoBMT) for multiple myeloma (MM). *Blood* 1989; 74 (Suppl. 1): 202a.
32. Turhan A, Eaves CJ, Humphries RK, Shepherd J, **Klingemann HG**, Eaves AC. Molecular and cellular analysis of GM-CSF induced hemopoietic recovery in a patient with clonal aplasia. *Proc Am Assoc Cancer Res* 1989; 30: 327.
33. Turhan A, Eaves CJ, Humphries RK, Shepherd J, **Klingemann HG**, Eaves AC. Molecular and cellular analysis of GM-CSF induced hemopoietic recovery in a patient with clonal aplasia. *Clin Invest Med* 1989; 12 (Suppl. B): 45.
34. Barnett MJ, Eaves CJ, Phillips GL, Hogge DE, Humphries RK, Kalousek DK, **Klingemann H-G**, Lansdorp PM, Reece DE, Shaw GJ, Shepherd JD, Eaves AC. Autografting in chronic myeloid leukemia (CML) with cultured marrow: Consistent restoration of Philadelphia chromosome (Ph¹)-negative hematopoiesis in patients selected by prior assessment of their marrow in vitro. *Blood* 1990; 76 (Suppl. 1): 526a.

35. Barnett MJ, Eaves CJ, Phillips GL, Humphries RK, Kalousek DK, **Klingemann H-G**, Lansdorp PM, Reece DE, Shaw GJ, Shepherd JD, Turhan AG, Eaves AC. Autografting in chronic myeloid leukemia (CML) after maintenance of marrow in culture. *J Cell Biochem* 1990 ; (Suppl. 14A): 305.
36. Barnett MJ, Eaves CJ, Phillips GL, Humphries RK, Kalousek DK, **Klingemann H-G**, Lansdorp PM, Reece DE, Shaw GJ, Shepherd JD, Turhan AG, Eaves AC. Autografting with curative intent in chronic myeloid leukemia (CML). *Exp Hematol* 1990; 18: 705.
37. Barnett MJ, Eaves CJ, Phillips GL, Humphries RK, Kalousek DK, **Klingemann H-G**, Lansdorp PM, Reece DE, Shaw GJ, Shepherd JD, Turhan AG, Eaves AC. Treatment of chronic myeloid leukemia (CML) with intensive therapy and transplantation of cultured autologous marrow. *Clin Invest Med* 1990; 13 (Suppl. B): 44.
38. Barnett MJ, Swenerton KD, Hoskins PJ, Klimo P, **Klingemann H-G**, Reece DE, Shepherd JD, Phillips GL. Intensive therapy with carboplatin, etoposide and melphalan (CEM) and autologous stem cell transplantation (SCT) for epithelial ovarian carcinoma (EOC). *Proc Am Soc Clin Oncol* 1990; 9: 168.
39. Barnett MJ, Swenerton KD, Hoskins PJ, Klimo P, **Klingemann H-G**, Reece DE, Shepherd JD, Phillips GL. High dose carboplatin, etoposide and melphalan (CEM) and autologous stem cell transplantation (SCT) for epithelial ovarian carcinoma (EOC). *Clin Invest Med* 1990; 13 (Suppl. B): 70.
40. Coppin CML, Barnett MJ, Murray N, **Klingemann H-G**, Reece DE, Shepherd JD, Phillips GL. High dose chemotherapy with autologous marrow rescue as consolidation for extreme risk non-seminoma. *Proc Am Soc Clin Oncol* 1990; 9: 139.
41. Elmongy MB, Barnett MJ, **Klingemann H-G**, Lansdorp P, Reece DE, Shepherd JD, Phillips GL. A phase I/II study of the treatment of acute myelogenous leukemia (AML) using busulfan (BU) and carboplatin (CBCDA) conditioning and 4 hydroperoxycyclophosphamide (4-HC) purged autologous bone marrow transplantation (BMT). *Clin Invest Med* 1990; 13 (Suppl. B): 45.
42. Gong N, **Klingemann H-G**. The role of adhesion molecules in lymphokine-activated killer (LAK) cell generation and tumor target cell killing. *Blood* 1990; 76 (Suppl. 1): 207a.
43. Grigg AP, Barnett MJ, Reece DE, Shepherd JD, **Klingemann H-G**, Phillips GL. Ineffectiveness of allogeneic bone marrow transplantation (AlloBMT) for acute myeloid leukemia (AML) relapsing after, or refractory to, high dose Ara-C (HD Ara-C). *Blood* 1990; 76 (Suppl. 1): 543a.
44. Grigg AP, Phillips GL, Barnett MJ, Buskard NA, Reece DE, Shepherd JD, **Klingemann H-G**. CMV hyperimmunoglobulin after allogeneic bone marrow transplantation. *J Cell Biochem* 1990 ; (Suppl. 14A): 308.
45. Grigg AP, Wolber R, Erb S, Barnett MJ, Reece DE, Shepherd JD, Phillips GL, **Klingemann H-G**. The significance of cytomegalovirus isolated from gastrointestinal endoscopy after bone marrow transplantation. *Bone Marrow Transplant* 1990; 5 (Suppl. 2): 64.
46. **Klingemann H-G**, Barnett MJ, Reece DE, Shepherd JD, Phillips GL. Use of an immunoglobulin preparation enriched for IgA and IgM (Pentaglobin[®]) in the treatment of acute GVHD. *Bone Marrow Transplant* 1990; 5 (Suppl. 2): 120.
47. Kohn F, Grigg ME, **Klingemann H-G**. Regulation of fibronectin receptor (FN-R; VLA-5) gene expression in human peripheral blood mononuclear cells (PBMC). *J Cell Biochem* 1990; (Suppl. 14A): 166.
48. Kohn FR, **Klingemann H-G**. Regulation of fibronectin receptor ($\alpha 5 \beta 1$) gene expression in cultured human monocytes and macrophages. *Exp Hematol* 1990; 18: 562.

COPY

49. Kohn FR, Phillips GL, **Klingemann H-G**. Analysis of cytokine-induced TNF- α production by monocytes offers new therapeutic potential for bone marrow transplant (BMT) recipients. *Blood* 1990; 76 (Suppl. 1): 549a.
50. Nevill TJ, Barnett MJ, **Klingemann H-G**, Reece DE, Shepherd JD, Phillips GL. Regimen-related toxicity of busulfan and cyclophosphamide conditioning in 71 patients undergoing allogeneic bone marrow transplantation. *Clin Invest Med* 1990; 13 (Suppl. B): 45.
51. Nevill TJ, Reece DE, **Klingemann H-G**, Shepherd JD, Barnett MJ, Phillips GL. Regimen-related toxicity (RRT) of a busulfan-cyclophosphamide (BUCY) conditioning regimen in 75 patients (pts) undergoing allogeneic bone marrow transplantation (BMT). *Blood* 1990; 76 (Suppl. 1): 557a.
52. Nevill TJ, Shepherd JD, Reece DE, Barnett MJ, **Klingemann H-G**, Phillips GL. Treatment of myelodysplastic syndromes (MDS) with busulfan-cyclophosphamide (BUCY) conditioning and allogeneic bone marrow transplantation (BMT). *Blood* 1990; 76 (Suppl. 1): 557a.
53. Reece D, Barnett M, Bow E, **Klingemann H-G**, Shepherd J, Shore T, Phillips G. High-dose cytosine arabinoside (HD ARA-C), etoposide (VP-16) and daunorubicin (DNR) for induction and consolidation therapy of adult acute myelogenous leukemia (AML). *Clin Invest Med* 1990; 13 (Suppl. B): 48.
54. Reece D, Barnett M, Chan K, Connors J, Fairey R, **Klingemann H-G**, O'Reilly S, Shepherd J, Voss N, Phillips G. Augmented cyclophosphamide (C), BCNU (B), VP-16-213 by continuous infusion (Vi) and cisplatin (P) and autologous bone marrow transplantation (AuBMT) in progressive Hodgkin's disease (HD). *Blood* 1990; 76 (Suppl. 1): 369a.
55. Reece DE, Barnett M, Bow E, **Klingemann H-G**, Shepherd J, Shore T, Phillips G. High dose cytosine arabinoside (HD Ara-C), etoposide (VP-16) and daunorubicin (DNR) as initial induction and consolidation therapy for adult acute myelogenous leukemia (AML). *Blood* 1990; 76 (Suppl. 1): 312a.
56. Reece DE, Elmongy MB, Barnett MJ, **Klingemann H-G**, Shepherd JD, Phillips GL. Induction chemotherapy (CT) with high-dose cytosine arabinoside (HDARA-C) and mitoxantrone (MXT) for poor prognosis acute (AML) and chronic (CML) myeloid leukemias. *Proc Am Soc Clin Oncol* 1990; 9: 207.
57. Shepherd JD, Pringle LE, Barnett MJ, **Klingemann H-G**, Reece DE, Phillips GL. 2-Mercaptoethane sulfonate (Mesna) vs hyperhydration (HH) for the prevention of cyclophosphamide induced hemorrhagic cystitis in bone marrow transplantation. *Proc Am Soc Clin Oncol* 1990; 9: 12.
58. Tirgan MH, Nevill TJ, **Klingemann H-G**, Reece DE, Shepherd JD, Barnett MJ, Phillips GL. Cyclosporine (CSP), methotrexate (MTX) and folinic acid rescue (FAR) for amelioration of toxicity after allogeneic bone marrow transplantation. *Blood* 1990; 76 (Suppl. 1): 569a.
59. Barnett MJ, Coppin CML, Murray N, Nevill TJ, **Klingemann H-G**, Reece DE, Shepherd JD, Phillips GL. Intensive therapy and autologous bone marrow transplantation (BMT) for patients with poor prognosis nonseminomatous germ cell tumors. *Proc Am Soc Clin Oncol* 1991; 10: 165.
60. Bredeson C, Barnett M, Dalal BI, Eaves A, Horsman D, **Klingemann H-G**, Nantel S, Ragaz J, Reece D, Shepherd J, Phillips GL. Secondary acute myelogenous leukemia (AML) at the Vancouver General Hospital (VGH) from 1986 to 1990. *Blood* 1991; 78 (Suppl. 1): 449a.
61. Elmongy M, Nevill T, Barnett M, Reece D, Shepherd J, **Klingemann H-G**, Phillips G. Etoposide (VP-16), cyclophosphamide (CY) and total body irradiation (TBI) conditioning and donor bone marrow transplantation (BMT) for lymphoid malignancies. *Clin Invest Med* 1991; 14 (Suppl. A): 60.

COPY

62. Elmongy MB, Barnett MJ, Bow E, **Klingemann H-G**, Reece DE, Shepherd JD, Shore T, Phillips GL. Allogeneic bone marrow transplantation (BMT) vs high dose cytarabine (HIDAC)-based chemotherapy (CTX) regimens in first remission acute myeloid leukemia (AML). Proc Am Soc Clin Oncol 1991; 10: 227.
63. Elmongy MB, Nevill TJ, **Klingemann H-G**, Shepherd JD, Reece DE, Barnett MJ, Nantel SH, Phillips GL. Cyclosporine (CSA) and methotrexate (MTX) vs CSA and methylprednisolone (MP) for graft-vs-host disease (GVHD) prophylaxis. Blood 1991; 78 (Suppl. 1): 233a.
64. Elmongy MB, Reece DE, Barnett MJ, Shepherd JD, Nantel SH, **Klingemann H-G**, Bow E, Shore T, Phillips GL. Comparative study of bone marrow transplantation (BMT) vs high dose cytarabine (HIDAC)-based chemotherapy (CTX) regimens in first remission acute myeloid leukemia (AML). Blood 1991; 78 (Suppl. 1): 233a.
65. Elmongy MB, Shepherd JD, Reece DE, Barnett MJ, **Klingemann H-G**, Phillips GL. Busulfan (BU)-cyclophosphamide (CY) conditioning and allogeneic bone marrow transplantation (BMT) for acute myeloid leukemia (AML). Proc Am Soc Clin Oncol 1991; 10: 228.
66. Elmongy MB, Shepherd JD, Reece DE, Barnett MJ, **Klingemann H-G**, Phillips GL. Second bone marrow transplantation (BMT) for patients (pts) with hematologic malignancy who relapse following first BMT. Clin Invest Med 1991; 14 (Suppl. A): 59.
67. **Klingemann H-G**, Deal H, Gong H, Reid D, Eaves CJ. Incubation of bone marrow autografts to allow generation ex vivo of lymphokine (IL-2)-activated killer (LAK) cells. Onkologie 1991; 14 (Suppl. 2): 86.
68. **Klingemann H-G**, Eaves AC, Onetto N, Wilkie-Boyd K, Barnett MJ, Connors J, Reece DE, Shepherd JD, Phillips GL. Randomized trial of GM-CSF (2 hour versus 24 hour infusion) after autologous bone marrow transplantation (AuBMT) for Hodgkin's disease. Exp Hematol 1991; 19: 558.
69. **Klingemann H-G**, Eaves AC, Onetto N, Wilkie-Boyd K, Barnett MJ, Connors J, Reece DE, Shepherd JD, Phillips GL. Randomized trial of GM-CSF (2 hour versus 24 hour infusion) after autologous bone marrow transplantation (AuBMT) for Hodgkin's disease. Clin Invest Med 1991; 14 (Suppl. A): 60.
70. **Klingemann H-G**, Eaves CJ, Eaves AC, Nantel SH, Barnett MJ, Reece DE, Shepherd JD, Phillips GL. Transplantation of autologous bone marrow cultured in interleukin 2 to support myeloablative chemotherapy in poor prognosis acute myeloid leukemia (AML). Blood 1991; 78 (Suppl. 1): 236a.
71. **Klingemann H-G**, Grigg A, Eaves AC, Wilkie-Boyd K, Barnett MJ, Reece DE, Shepherd JD, Phillips GL. Interferon after bone marrow transplantation for patients at high risk of relapse. Proc Am Soc Clin Oncol 1991; 10: 228.
72. **Klingemann H-G**, Grigg A, Eaves AC, Wilkie-Boyd K, Barnett MJ, Reece DE, Shepherd JD, Phillips GL. Interferon after bone marrow transplantation for patients at high risk of relapse. Clin Invest Med 1991; 14 (Suppl. A): 59.
73. Nantel SH, Barnett MJ, Chow E, Benny WB, Reece DE, Naiman SC, Shepherd JD, **Klingemann H-G**, Phillips GL. Combined severe coagulopathy with platelet dysfunction and reversible factor X (FX) deficiency in a patient with multiple myeloma (MM). Blood 1991; 78 (Suppl. 1): 485a.
74. Nantel SH, Reece DE, Shepherd JD, **Klingemann H-G**, Barnett MJ, Dalal BI, Horsman D, Phillips GL. B cell acute lymphoblastic leukemia (ALL-L3) post 4-hydroperoxycyclophosphamide (4HC) purged autologous bone marrow transplant (ABMT) for multiple myeloma (MM). Blood 1991; 78 (Suppl. 1): 127a.

COPY

75. Nevill T, Barnett M, Reece D, Shepherd J, Chan K, **Klingemann H**, Phillips G. Bone marrow transplantation (BMT) for lymphoid malignancies utilizing a cyclophosphamide (CY) and total body irradiation (TBI) conditioning regimen intensified with etoposide (VP-16). *Proc Am Soc Clin Oncol* 1991; 10: 279.
76. Nevill TJ, Barnett MJ, Chan K, **Klingemann H-G**, Nantel SH, Reece DE, Shepherd JD, Messner HA, Meharchand J, Phillips GL. Efficacy of combined cyclosporine (CSP), methotrexate (MTX) and XomaZyme-H65 prophylaxis for patients (pts) at high risk of acute graft-versus-host disease (GVHD) after allogeneic bone marrow transplantation (BMT). *Blood* 1991; 78 (Suppl. 1): 233a.
77. Nevill TJ, Elmongy MB, Shepherd JD, Reece DE, **Klingemann H-G**, Barnett MJ, Nantel SH, Phillips GL. The influence of donor parity on the incidence of graft-versus-host disease (GVHD), relapse and event-free survival (EFS) in patients (pts) undergoing allogeneic bone marrow transplantation (BMT). *Blood* 1991; 78 (Suppl. 1): 233a.
78. Nevill TJ, Tirgan MH, **Klingemann H-G**, Reece DE, Shepherd JD, Barnett MJ, Phillips GL. Influence of post-methotrexate (MTX) folinic acid rescue (FAR) on regimen-related toxicity (RRT) and incidence of acute graft-versus-host disease (GVHD) after allogeneic bone marrow transplantation (BMT). *Clin Invest Med* 1991; 14 (Suppl. A): 60.
79. Phillips GL, Barnett MJ, **Klingemann H-G**, Nantel SH, Reece DE, Shepherd JD. The use of unrelated-donor bone marrow transplantation (UD-BMT) in patients with acute leukemia (AL) and refractory anemia with excess blasts (RAEB). *Blood* 1991; 78 (Suppl. 1): 235a.
80. Phillips GL, Reece DE, Barnett MJ, Shepherd JD, **Klingemann H-G**. The use of unrelated-donor bone marrow transplantation (UD-BMT): Vancouver experience. *Exp Hematol* 1991; 19: 572.
81. Phillips GL, Reece DE, Barnett MJ, Shepherd JD, **Klingemann H-G**. The use of unrelated-donor bone marrow transplantation (UD-BMT): Vancouver experience. *Clin Invest Med* 1991; 14 (Suppl. A): 59.
82. Reece D, Barnett M, Connors J, **Klingemann H-G**, O'Reilly S, Shepherd J, Phillips G. Intensive chemotherapy (CT) with busulfan, cyclophosphamide and melphalan (BU + CY + MEL) and hematopoietic stem cell transplantation (HSCT) in patients (pts) with multiple myeloma (MM). *Proc Am Soc Clin Oncol* 10: 304, 1991.
83. Reece DE, Barnett MJ, Connors J, Fairey R, **Klingemann H-G**, O'Reilly S, Shepherd JD, Spinelli JJ, Voss N, Phillips GL. Intensive therapy with cyclophosphamide, BCNU, VP-16-213 ± cisplatin (CBV±P) and autologous bone marrow transplantation (AuBMT) for advanced Hodgkin's disease (HD): Outcome and prognostic factors in 90 patients (pts). *Blood* 1991; 78 (Suppl. 1): 273a.
84. Shepherd JD, Reece DE, **Klingemann H-G**, Barnett MJ, Phillips GL. Acute myeloid leukemia (AML) in patients (pts) over 60: Induction and consolidation therapy with moderate dose cytosine arabinoside, mitoxantrone, and etoposide. *Proc Am Soc Clin Oncol* 1991; 10: 228.
85. Shepherd JD, Reece DE, **Klingemann H-G**, Barnett MJ, Phillips GL. Acute myeloid leukemia (AML) in patients (pts) over 60: Induction and consolidation therapy with moderate dose cytosine arabinoside, mitoxantrone, and etoposide. *Haematologica* 1991; 76 (Suppl. 4): 90.
86. Sutherland HJ, Hogge DE, **Klingemann H-G**, Barnett MJ, Eaves AC, Eaves CJ. Cytokines as differentiating agents in hematopoiesis. *Cancer Invest* 1991; 10 (Suppl. 1): 3.
87. Barnett M, Nantel S, Eaves A, Eaves C, Reece D, **Klingemann H**, Shepherd J, Brockington D, Phillips G. Strategy to improve the utility of bone marrow transplantation (BMT) for patients (pts) with chronic myeloid leukemia (CML) in British Columbia (BC). *J Cell Biochem* 1992 ; (Suppl. 16A): 193.

COPY

88. Barnett MJ, Eaves CJ, Phillips GL, Hogge DE, **Klingemann HG**, Lansdorp PM, Nantel SH, Reece DE, Shepherd JD, Sutherland HJ, Eaves AC. Autografting in chronic myeloid leukemia with cultured marrow: Treatment of cytogenetic relapse with alpha-interferon. J Interferon Res 1992; 12 (Suppl. 1): S68.
89. Barnett MJ, Nantel SH, Bredeson CNA, Eaves AC, Eaves CJ, **Klingemann H-G**, Reece DE, Shepherd JD, Sutherland HJ, Phillips GL. A population-based study in British Columbia of bone marrow transplantation for patients with chronic myeloid leukemia. Blood 1992; 80: 66a.
90. Elmongy MB, Shepherd JD, Barnett MJ, Reece DE, Nantel SH, **Klingemann H-G**, Phillips GL. Busulfan (BU)-cyclophosphamide (CY) conditioning and allogeneic bone marrow transplantation (BMT) for chronic myeloid leukemia (CML). J Cell Biochem 1992 ; (Suppl. 16A): 196.
91. Gong J, Thacker JD, **Klingemann H-G**. Use of IL-2 activated bone marrow to eliminate minimal residual acute myeloid leukemia prior to autologous marrow transplantation. Exp Hematol 1992; 20: 728.
92. Gong JH, **Klingemann H-G**. Characterization of a human cell line with phenotypical and functional characteristics of activated natural killer cells. Blood 1992; 80 (Suppl. 1): 141a.
93. Nevill T, Barnett M, Chan K, **Klingemann H-G**, Nantel S, Reece D, Shepherd J, Messner H, Meharchand J, Phillips G. Efficacy of combined cyclosporine (CSP), methotrexate (MTX) and XomaZyme-H65 prophylaxis for patients (pts) at high risk of acute graft-versus-host disease (GVHD) after allogeneic bone marrow transplantation (BMT). J Cell Biochem 1992 ; (Suppl. 16A): 209.
94. Nevill TJ, Sayegh A, Elmongy MB, Reece DE, **Klingemann H**, Barnett MJ, Nantel SH, Shepherd JD, Phillips GL. Favourable event-free survival (EFS) for patients undergoing bone marrow transplantation (BMT) from a parous (P) female (F) donor. Clin Invest Med 1992 ; (Suppl. 15): A59.
95. Nevill TJ, Shepherd JD, Reece DE, **Klingemann H**, Barnett MJ, Nantel SH, Phillips GL. Treatment of myelodysplastic syndrome (MDS) with allogeneic bone marrow transplantation (BMT): The Vancouver experience. Clin Invest Med 1992; (Suppl. 15): A59.
96. Phillips GL, Reece DE, Barnett MJ, **Klingemann H-G**, Nantel SH, Shepherd JD, Sutherland H, Spinelli JJ. Allogeneic bone marrow transplantation (BMT) for multiple myeloma (MM): The Vancouver experience. Clin Invest Med 1992; 15: A59.
97. Reece DE, Barnett MJ, Chan K, **Klingemann H-G**, Nantel SH, Shepherd JD, Spinelli JJ, Sutherland HJ, Phillips GL. Chronic graft-versus-host disease (CGVHD) in patients (pts) receiving unrelated donor (UD) allogeneic bone marrow transplants (allo BMTs): Incidence, risk factors and outcome. Clin Invest Med 1992; 15: A61.
98. Reece DE, Shepherd JD, **Klingemann H-G**, Barnett MJ, Chan K, Nantel SH, Phillips GL. Allogeneic bone marrow transplantation (BMT) using unrelated donors (UDS): The Vancouver experience. J Cell Biochem 1992; (Suppl. 16A): 210.
99. Reece DE, Shepherd JD, Nantel SH, Barnett MJ, Spinelli JJ, Sutherland HJ, **Klingemann H-G**, Phillips GL. Intensive therapy (IT) and allogeneic bone marrow transplantation (AlloBMT) for multiple myeloma (MM) patients (Pts): The Vancouver experience. Blood 1992; 80: 362a.
100. Sayegh A, Barnett MJ, Shepherd JD, Chan K, Dalal BI, Nantel SH, Reece DE, **Klingemann H-G**, Sutherland HJ, Phillips GL. Intensive therapy and autografting with 4-hydroperoxycyclophosphamide-treated marrow for poor-prognosis acute lymphoblastic leukemia. Blood 1992; 80: 206a.

COPY

101. Sayegh A, Reece D, Barnett M, Connors J, Shepherd J, Fairey R, O'Reilly S, Nantel S, **Klingemann H-G**, Spinelli J, Voss N, Phillips G. Interstitial pneumonitis (IP) following high-dose chemotherapy (CT) with cyclophosphamide, BCNU, etoposide \pm cisplatin (CBV \pm P) and autologous bone marrow transplantation for advanced Hodgkin's disease (HD): Incidence, risk factors and outcome. J Cell Biochem 1992; (Suppl. 16A): 205.
102. Shepherd JD, Barnett MJ, Connors JM, Spinelli JJ, Sutherland HJ, **Klingemann HG**, Nantel SH, Reece DE, Currie CJ, Phillips GL. Allogeneic bone marrow transplantation for poor prognosis non-Hodgkin's lymphoma (NHL). Blood 1992; 80: 67a.
103. Toze C, Barnett MJ, **Klingemann H-G**. Response of therapy-related refractory anemia with excess blasts (RAEB) to low dose interleukin-2 (IL-2). Exp Hematol 1992; 20: 712.
104. Toze C, Reece DE, Barnett MJ, **Klingemann H-G**, Shepherd JD, Nantel SH, Sutherland HJ, Spinelli JJ, Phillips GL. Acalculous cholecystitis (AC) in bone marrow transplant (BMT) and chemotherapy (CT) patients (Pts). Blood 1992; 80: 139a.
105. Toze CL, Reece DE, Barnett MJ, **Klingemann H-G**, Nantel SH, Shepherd JD, Spinelli JJ, Sutherland H, Phillips GL. Cytomegalovirus (CMV) infection in allogeneic bone marrow transplant (allo BMT) patients (pts) in Vancouver. Clin Invest Med 1992; 15 (Suppl. A): 56.
106. Bardy P, Phillips GL, Barnett MJ, Eaves CJ, Lansdorp P, Thomas TE, **Klingemann H-G**. Successful engraftment after graft failure following unrelated donor (UD) allograft depleted of T-cells for chronic idiopathic myelofibrosis (CIM). Exp Hematol 1993; 21: 1131.
107. Bredeson CN, Barnett MJ, Dalal BI, Nantel SH, Shepherd JD, Sutherland HJ, **Klingemann H-G**, Reece DE, Phillips GL. High dose cytarabine (HDARAC) therapy of patients (pts) with hypoplastic acute myelogenous leukemia (AML). Clin Invest Med 1993; 16 (Suppl. B): 63.
108. Elmongy MB, Nantel SH, Reece DE, Barnett MJ, Shepherd JD, **Klingemann H-G**, Sutherland H, Embree L, Phillips GL. Autologous bone marrow transplantation (BMT) for acute myeloid leukemia (AML) using combined carboplatin (CBDCA) and busulfan (BU). A phase I/II study. Proc Am Soc Clin Oncol 1993; 12: 312.
109. Elmongy MB, Nantel SH, Reece DE, Barnett MJ, Shepherd JD, **Klingemann H-G**, Sutherland H, Embree L, Phillips GL. Carboplatin (CBDCA) and busulfan (BU) and autologous bone marrow transplantation (BMT) for therapy of acute myeloid leukemia (AML). Clin Invest Med 1993; 16 (Suppl. B): B63.
110. Embree L, Burns RB, Fung HC, Heggie JR, O'Brien RK, Spinelli JJ, Reece D, Barnett MJ, Shepherd JD, Sutherland H, Nantel S, **Klingemann H**, Phillips GL. Busulfan clinical pharmacodynamics in bone marrow transplantation (BMT) patients. Pharm Res 1993; 12 (Suppl. 9): S411
111. Embree L, Heggie JH, Reece D, Shepherd J, Barnett M, Nantel S, **Klingemann H**, Hartley DO, Hudon NJ, Spinelli JJ, Bredeson C, Tezcan H, Sayegh T, Russell J, Eaket L, Walker J, Runzer N, Phillips GL. Relationship between first-dose pharmacokinetics and steady-state busulfan concentrations. Proc Am Assoc Cancer Res 1993; 34: 392
112. Embree L, Spinelli JJ, Reece DE, Shepherd JD, Barnett MJ, Nantel S, **Klingemann H**, Heggie JH, Hudon NJ, Hartley DO, Burns RB, Phillips GL. Association between busulfan AUC and hepatotoxicity. Pharm Res 1993; 10 (Suppl. 10): S353
113. Fung H, Shepherd JD, **Klingemann H-G**, Nantel SH, Barnett MJ, Reece DE, Sutherland HJ, Spinelli JJ, Phillips GL. Assessment of non-relapse mortality (NRM) in older patients undergoing bone marrow transplantation. Blood 1993; 82: 291a.

COPY

114. Fung H, Shepherd JD, Naiman SC, Barnett MJ, Reece DE, Horsman DE, Nantel SH, Sutherland HJ, Spinelli JJ, **Klingemann H-G**, Phillips GL. Acute monocytic leukemia: A single institution experience. *Blood* 1993; 82: 58a.
115. **Klingemann H-G**, Eaves CJ, Barnett MJ, Eaves AC, Hogge DE, Lansdorp PM, Nantel SH, Reece DE, Shepherd JD, Sutherland HJ, Phillips GL. Transplantation of patients with high risk acute myeloid leukemia (AML) in first remission with autologous marrow cultured in interleukin-2 followed by interleukin-2 in vivo. *Exp Hematol* 1993; 21: 1063.
116. **Klingemann HG**, Barnett MJ, Eaves AC, Eaves CJ, Hogge DE, Lansdorp PM, Nantel SH, Reece DE, Shepherd JD, Sutherland H, Phillips GL. Transplantation of interleukin-2-activated autologous bone marrow in patients with acute myeloid leukemia (AML). Proceedings of the 19th Annual Meeting of the EBMT and 9th Meeting of the Nurses Group, Garmisch-Partenkirchen, Germany. 1993; January 17-21, 122.
117. Reece D, Barnett M, Connors J, Fairey R, **Klingemann H**, Nantel S, O'Reilly S, Shepherd J, Spinelli J, Sutherland H, Voss N, Phillips G. Intensive therapy with cyclophosphamide, BCNU, etoposide \pm cisplatin (CBV \pm P) and autologous bone marrow transplantation for patients with Hodgkin's disease in first relapse. Proceedings of the 5th International Lymphoma Meeting, Lugano, 1993, June 9-12.
118. Reece D, Billadeau D, Van Ness B, Barnett M, **Klingemann H-G**, Nantel S, Shepherd J, Sutherland H, Phillips G. Intensive therapy (IT) and allogeneic bone marrow transplantation (alloBMT) in multiple myeloma (MM): Preliminary clinical and molecular results. Proceedings of the IV International Workshop on Multiple Myeloma, Mayo Medical Center, Rochester, Minnesota, 1993; October 2-5, 147.
119. Reece DE, Nantel SH, Sutherland HJ, **Klingemann H-G**, Barnett MJ, Shepherd JD, Phillips GL. Multi-phase therapy of multiple myeloma (MM) using high-dose busulfan, melphalan and cyclophosphamide (BU+MEL+CY) followed by autologous bone marrow transplantation (AUBMT) with 4-hydroperoxycyclophosphamide (4-HC) purging. *Blood* 1993; 82: 266a.
120. Shepherd JD, Sutherland HJ, Reece DE, Barnett MJ, **Klingemann H-G**, Nantel SH, Wilkie-Boyd KE, Currie CJ, Spinelli JJ, Phillips GL. Utility of chest xray and ancillary investigations in febrile neutropenic patients. *Blood* 1993; 82: 423a.
121. Tezcan H, Barnett M, Reece D, Shepherd J, Dalal B, Horsman D, **Klingemann H-G**, Nantel S, Sutherland H, Phillips G. Treatment of acute promyelocytic leukemia in patients presenting at Vancouver General Hospital from 1983 to 1992. *Proc Am Soc Clin Oncol* 1993; 12: 307.
122. Tezcan H, Bredeson CN, Barnett MJ, McGraw RW, **Klingemann H-G**, Nantel SH, Reece DE, Shepherd JD, Spinelli JJ, Sutherland HJ, Phillips GL. Avascular necrosis of bone is a frequent complication of unrelated donor bone marrow transplantation. *Blood* 1993; 82: 643a.
123. Bardy PG, Nantel SH, Shepherd JD, **Klingemann H-G**, Barnett MJ, Spinelli JJ, Reece DE, Sutherland HJ, Phillips GL. Acute peri-engraftment syndrome: A distinct syndrome complicating volunteer unrelated-donor (VUD) allogeneic bone marrow transplantation (BMT). Proceedings of the 20th EBMT Meeting, Bone Marrow Transplant: 1994; 128.
124. Fung H, Barnett M, Reece D, **Klingemann H**, Shepherd J, Nantel S, Sutherland H, Spinelli J, Phillips G. Delayed complications of volunteer unrelated donor bone marrow transplantation (VUD-BMT). *Blood* 1994; 84: 492a.
125. Jackson SR, Shepherd JD, Tweeddale MG, Barnett MJ, Spinelli JJ, Sutherland HJ, Reece DE, **Klingemann H-G**, Nantel SH, Phillips GL. Admission of bone marrow transplant (BMT) recipients to the intensive care unit (ICU). *Blood* 1994; 84: 485a.

COPY

126. **Klingemann H-G**, Barnett MJ, Eaves AC, Eaves CJ, Hogge DE, Lansdorp PM, Nantel SH, Reece DE, Shepherd JD, Sutherland H, Phillips GL. Transplantation of interleukin-2-activated autologous bone marrow in patients with acute myeloid leukemia (AML). Bone Marrow Transplant 1994; 14: 389.
127. **Klingemann H-G**, Wong E, Maki G, Phillips GL. A cytotoxic NK-cell clone for effective immunological purging of leukemic cells from blood. Blood 1994; 84: 498.
128. Kühr T, Dougherty G, **Klingemann H-G**. Transfer of the TNF-alpha gene into hematopoietic progenitor cells as a model for site specific cytokine delivery after marrow transplantation. Exp Hematol 1994; 22: 818.
129. Maki G, Gong JH, Dougherty GJ, Takei F, **Klingemann H-G**. Characterization of a human cell line with characteristics of activated natural killer cells to study natural killer cell-leukemic cell interactions. Nat Immun Cell Growth Regul 1994; 13: 229.
130. Phillips G, Barnett M, Reece D, Sutherland H, Nantel S, Shepherd J, **Klingemann H-G**, Spinelli J. Impact of donor source on outcome after allogeneic bone marrow transplantation (BMT) for chronic myelogenous leukemia (CML) in initial stable phase (SP). Proc Am Soc Clin Oncol 1994; 13: 306.
131. Reece D, Nantel S, Sutherland H, **Klingemann H-G**, Barnett M, Shepherd J, Spinelli J, Phillips G. Intensive therapy of multiple myeloma (MM) utilizing autologous 4-hydroperoxycyclophosphamide (4-HC) purged autologous bone marrow transplantation (AuBMT). Second Clinical Conference of the International Myeloma Foundation, Singapore, 1994; March 2-5.
132. Reece D, Spinelli J, Barnett M, Connors J, Hogge D, **Klingemann H**, Fairey R, Klasa R, Nantel S, O'Reilly S, Shepherd J, Voss N, Sutherland H, Phillips G. High-dose cyclophosphamide, BCNU, VP16-213 ± cisplatin (CBV±P) and autologous stem cell transplantation (ASCT) for patients (PTS) with Hodgkin's disease (HD) who fail to enter a complete remission (CR) after combination chemotherapy. Blood 1994; 84: 162a.
133. Reece D, Thomas T, Lansdorp P, Barnett M, Nantel S, Sutherland H, Spinelli J, Shepherd J, **Klingemann H**, Phillips G. A preliminary analysis of intensified conditioning (IC) followed by transplantation of allogeneic bone marrow (ALLOBMT) depleted of CD3⁺ cells using high gradient magnetic separation (HGMS) in patients (PTS) receiving unrelated donor (UD) grafts. Blood 1994; 84: 342a.
134. Shepherd JD, Reece DE, Barnett MJ, Nantel SH, **Klingemann H-G**, Sutherland HJ, Spinelli JJ, Phillips GL. Induction chemotherapy with continuous infusion ara-C, mitoxantrone, and VP-16 for patients £65 with acute myeloid leukemia. Proc Am Soc Clin Oncol 1994; 13: 308.
135. Toze CL, Barnett MJ, **Klingemann H-G**, Nantel SH, Reece DE, Shepherd JD, Sutherland HJ, Phillips GL. Preventative strategies for cytomegalovirus (CMV) interstitial pneumonitis (IP) post allogeneic bone marrow transplant (allo-BMT): A decision and cost analysis. Blood 1994; 84: 88a.
136. Wong E, Eaves C, Phillips GL, **Klingemann H-G**. Anti-leukemic activities of human bone marrow and blood cells after culture in IL-2, IL-7 and IL-12. Exp Hematol 1994; 22: 826.
137. Berkahn LC, Fung HC, Horsman DE, Le A, Nantel SH, Shepherd JD, Toze CL, Sutherland HJ, **Klingemann H-G**, Barnett MJ. Allogeneic Bone Marrow Transplantation (BMT) for adults with chronic myeloid leukemia (CML) in accelerated phase (AP). American Society of Hematology 37th Annual Meeting, 1995, Blood 1995; 86: 97a.
138. Forrest DL, Spinelli JJ, Naiman SC, Davis JH, Fung HC, **Klingemann H-G**, Nantel SH, Schultz KR, Shepherd JD, Sutherland HJ, Toze CL, Barnett MJ. Second malignant neoplasms after autografting: The Vancouver experience. American Society of Hematology 37th Annual Meeting, 1995, Blood 1995; 86: 400a.

COPY

139. Fung H, Shepherd J, Connors J, Nantel S, **Klingemann H**, Sutherland H, Reece D, Phillips G, Spinelli J, Gascoyne R, Barnett M. Intensive therapy with autologous bone marrow transplantation (AuBMT) for adults with high grade non-Hodgkin's lymphoma (HG-NHL). ASBMT First Annual Meeting, Keystone, CO, January 26-28, ASBMT Proceedings 1995; 66.
140. Fung HC, Barnett MJ, **Klingemann H-G**, Toze CL, Le A, Sutherland HJ, Phillips GL, Nantel SH, Reece DE, Shepherd JD. Assessment of non-relapse mortality (NRM) in older patients undergoing volunteer unrelated donor bone marrow transplantation (VUD-BMT). American Society of Hematology 37th Annual Meeting, Blood 1995; 86: 390a.
141. Fung HC, Barnett MJ, Shepherd JD, Nantel SH, Reece DE, **Klingemann H-G**, Sutherland HJ, Davis JH, Schultz KR, Spinelli JJ, Grigg AP, Phillips GL. Allogeneic bone marrow transplantation for patients with acute leukemia and refractory anemia with excess blasts in transformation for whom primary therapy failed to bring about complete remission. Royal College of Physicians and Surgeons of Canada Meeting, 1995, Clin Invest Med 1995; 18 (Suppl. 4): B63.
142. Fung HC, Coppin CML, Murray N, Shepherd JD, **Klingemann H-G**, Nantel SH, Sutherland HJ, Reece DE, Phillips GL, Barnett MJ. Intensive therapy with autografting for adults with poor prognosis germ cell tumors. Royal College of Physicians and Surgeons of Canada Meeting, 1995, Clin Invest Med 1995; 18 (Suppl. 4): B90.
143. Fung HC, Nantel SH, Phillips GL, Shepherd JD, Sutherland HJ, **Klingemann H-G**, Toze CL, Reece DE, Barnett MJ. Allogeneic bone marrow transplantation (BMT) for adults with secondary myelodysplastic syndrome (MDS) or secondary acute myelogenous leukemia (AML). American Society of Hematology 37th Annual Meeting, 1995, Blood 1995; 86: 96a.
144. Fung HC, Sayegh A, **Klingemann H-G**, Nantel SH, Shepherd JD, Chan K-W, Dalal BI, Horsman DE, Sutherland HJ, Reece DE, Phillips GL, Spinelli JJ, Barnett MJ. Intensive therapy and autografting with 4-hydroperoxycyclophosphamide treated marrow for patients with poor prognosis acute lymphoblastic leukemia. ISHAGE 2nd International Meeting, June 21-23, 1995, J Hematol 1995; 4: 248.
145. Fung HC, Voss NJ, Barnett MJ, Fairey RN, Reece DE, Phillips GL, Shepherd JD, Nantel SH, Sutherland HJ, Toze CL, **Klingemann H-G**. Low dose thoraco-abdominal irradiation for treatment of advanced chronic graft-versus-host disease. American Society of Hematology 37th Annual Meeting, 1995, Blood 1995; 86: 390a.
146. Keller O, Fung H, Shepherd J, Connors J, Nantel S, **Klingemann H**, Sutherland H, Reece D, Phillips G, Spinelli J, Gascoyne R, Barnett M. Intensive therapy with autologous or allogeneic bone marrow transplantation (BMT) for adults with high grade non-Hodgkin's lymphoma (NHL). Royal College of Physicians and Surgeons of Canada Meeting, 1995, Clin Invest Med 1995; 18 (Suppl. 4): B62.
147. Krance R, Hurwitz C, Heslop H, Santana V, Ribeiro R, Mahmoud H, Roberts W, **Klingemann H**, Ball E, Rill D, Brenner M. AML-91 pilot study: 1) to determine the response rate to 2 -CDA in previously untreated children with *de novo* AML and 2) to investigate the efficacy of autoBMT by the use of NEO^R gene marking. Blood 1995; 86: 433a.
148. Maki G, Dougherty G, Takei F, **Klingemann H**. Activation of protein tyrosine phosphorylation in the human NK cell line NK-92 via ICAM-3 and CD44. Nat Immun 1995; 14: 83.
149. McCarron BI, Muller NL, Ostrow DN, Fung HC, **Klingemann H-G**, Nantel SH, Shepherd JD, Sutherland HJ, Toze CL, Barnett MJ. Pulmonary hemorrhage complicating intensive therapy of malignant disease: Radiological findings. American Society of Hematology 37th Annual Meeting, Blood 1995; 86: 957a

COPY

150. Fung HC, Nantel SH, Phillips GL, Shepherd JD, Sutherland HJ, **Klingemann H-G**, Toze CL, Reece DE, Barnett MJ. Allogeneic bone marrow transplantation for adults with secondary myelodysplastic syndrome or secondary acute myelogenous leukemia. American Society of Hematology 37th Annual Meeting, Blood 1995; 86: 96a
151. Reece D, Shepherd J, Brockington D, Barnett M, Nantel S, **Klingemann H**, Sutherland H, Phillips G. Multiphase therapy involving purged autologous bone marrow transplantation (ABMT) for multiple myeloma (MM) patients (PTS). Vth International Workshop on Multiple Myeloma, Vth Int'l Workshop MM 1995.
152. Reece D, Shepherd J, Brockington D, Barnett M, Nantel S, **Klingemann H-G**, Sutherland H, Phillips G. Multiphase therapy involving 4-hydroperoxycyclophosphamide (4-HC) purged autologous bone marrow transplantation (ABMT) for multiple myeloma (MM) patients (pts). ASBMT First Annual Meeting, Keystone, CO, January 26-28, ASBMT Proceedings 1995; 101.
153. Shepherd JD, Barnett MJ, Brockington DA, Fung HC, **Klingemann H-G**, Nantel SH, Reece DE, Sutherland HJ, Thierman JG, Toze CL, Phillips GL. Induction and consolidation therapy with intermediate-dose cytarabine, mitoxantrone and etoposide in patients ≥ 60 years with acute myeloid leukemia (AML). American Society of Hematology 37th Annual Meeting, 1995, Blood 1995; 86: 522a
154. Shepherd JD, Reece DE, Shore TB, Barnett MJ, Bow EJ, Nantel SH, Sutherland HJ, Brockington DA, Fung HC, Spinelli JJ, **Klingemann H-G**, Phillips GL. High dose cytarabine, daunorubicin, and etoposide induction and consolidation therapy of acute myeloid leukemia in adults ≤ 60 years of age. Royal College of Physicians and Surgeons of Canada Meeting, 1995, Clin Invest Med 1995; 18 (Suppl. 4): B92.
155. Simpson DR, Fung HC, Ostrow DN, Shepherd JD, Nantel SH, Sutherland HJ, **Klingemann H-G**, Toze CL, Barnett MJ. Nebulised amphotericin B as an adjunct to high dose IV amphotericin B in the treatment of fungal pneumonia in immunocompromised patients: A pilot study. American Society of Hematology 37th Annual Meeting, 1995, Blood 1995; 86: 966a.
156. Simpson DR, Vickars LM, Fung HC, Naiman SC, Horsman DE, Shepherd JD, Nantel SH, Sutherland HJ, **Klingemann H-G**, Toze CL, Barnett MJ. Relapse of acute myelogenous leukemia (AML) at extramedullary sites after allogeneic bone marrow transplantation (BMT) with busulfan (BU) and cyclophosphamide (CY) conditioning. American Society of Hematology 37th Annual Meeting, 1995, Blood 1995; 86: 966a.
157. Tezcan H, Barnett MJ, Reece DE, Shepherd JD, Spinelli JJ, Sutherland HJ, Chan K-W, Nantel SH, **Klingemann H-G**, Phillips GL. Secondary treatment of acute graft-versus-host disease (GVHD) with anti-CD5 ricin a chain immunotoxin: a single institute experience. ASBMT First Annual Meeting, Keystone, CO, January 26-28, ASBMT Proceedings 1995; 79.
158. Toze CL, Shepherd JD, Sherlock CH, Nantel SH, Le A, Fung HC, Sutherland HJ, **Klingemann H-G**, Barnett MJ. Cytomegalovirus (CMV) disease (D) in allogeneic bone marrow transplant (BMT) recipients: Effectiveness of ganciclovir prophylactic strategy, characterization of CMV risk factors, and comparison to historical controls. American Society of Hematology 37th Annual Meeting, 1995, Blood 1995; 86: 968a.
159. Berkahn LC, Fung HC, Nantel SH, Shepherd JD, Sutherland HJ, **Klingemann H-G**, Toze CL, Eaves CJ, Eaves AC, Barnett MJ. Peri-engraftment syndrome after autografting with cultured marrow for chronic myeloid leukemia. Clin Invest Med 1996; 19 (Suppl. 4): S33.
160. Comeau TB, Barnett MJ, Fung HC, Toze CL, Shepherd JD, Nantel SH, Sutherland HJ, **Klingemann H-G**. Antithymocyte globulin in the management of steroid-resistant acute graft-versus-host disease. Clin Invest Med 1996; 19 (Suppl. 4): S32.

COPY

161. Comeau TB, Fung HC, Barnett MJ, Horsman DE, Toze CL, Nantel SH, Sutherland HJ, **Klingemann H-G**, Shepherd JD. Acute myelogenous leukemia with favorable cytogenetic abnormalities inv(16), t(8;21) -a 10 year experience at the Vancouver hospital. Clin Invest Med 1996; 19 (Suppl. 4): S34.
162. Forrest D, Fung H, Horsman D, Le A, Shepherd J, Toze C, Nantel S, Sutherland H, **Klingemann H**, Barnett M. Allogeneic bone marrow transplantation (BMT) for adults with primary myelodysplastic syndrome (MDS) - evaluation of prognostic factors. Clin Invest Med 1996; 19 (Suppl. 4): S33.
163. Forrest DL, Fung HC, Horsman DE, Shepherd JD, Nantel SH, Sutherland HJ, **Klingemann H-G**, Toze CL, Barnett MJ. Acute leukemia with 11q23 chromosomal abnormalities in adults. Clin Invest Med 1996; 19 (Suppl. 4): S34.
164. Fung HC, Shepherd JD, Nantel SH, Horsman DE, Le A, Forrest DE, Toze CL, Sutherland HJ, **Klingemann H**, Hogge DE, Barnett MJ. Allogeneic bone marrow transplantation for adults with primary myelodysplastic syndrome (MDS): evaluation of prognostic factors. American Society of Hematology, 38th Annual Meeting, Dec. 6-10, Orlando, FL, Blood 1996; 88: 480a.
165. **Klingemann H**, Tron V, Ho V. Preclinical studies with a highly cytotoxic cell line (NK-92) to prevent metastasis of malignant melanoma. Abstracts for the First Joint Meeting of the Japanese and Canadian Societies for Investigative Dermatology, J Dermatol Sci 1996; 12: 82.
166. Knight G, Nantel S, Shepherd J, Fung H, Sutherland H, Toze C, **Klingemann H**, Barnett M. Allogeneic bone marrow transplantation using unrelated donors for chronic myeloid leukemia in chronic phase. Clin Invest Med 1996; 19 (Suppl. 4): S33.
167. Maki G, Krystal G, Dougherty G, **Klingemann H-G**. Differential effects of cytokines in overcoming leukemic cell resistance to NK-cell mediated lysis: involvement of PKC activation through MAPK pathway. Blood 1996; 88: 314a.
168. Micallef INM, Barnett MJ, Davis JH, Schultz KR, **Klingemann H**, Shepherd JD, Sutherland HJ, Toze CL, Hogge DE, Pritchard SL, Munn KJ, Brockington DA, Fung HC, Rogers PCJ, Chan KW, Reece DE, Phillips GL, Nantel SH. A review of the Vancouver experience with bone marrow transplantation (BMT) using volunteer 1996; 88: 264a.
169. Micallef INM, Fung HC, Chhanabhai M, Gascoyne RD, Shepherd JD, Nantel SH, Toze CL, **Klingemann H-G**, Sutherland HJ, Barnett MJ. Epstein-Barr virus (EBV)-associated B-cell lymphoproliferative disorders (LPD) following bone marrow transplantation (BMT). Clin Invest Med 1996; 19 (Suppl. 4): S34.
170. Simpson DR, Barnett MJ, Fung HC, Nantel SH, Sutherland HJ, **Klingemann H-G**, Toze CL, Shepherd JD. Allogeneic bone marrow transplantation for multiple myeloma. Clin Invest Med 1996; 19 (Suppl. 4): S33.
171. Simpson DR, Phillips GL, Thomas TE, Lansdorp PM, Barnett MJ, Nantel SH, Shepherd JD, Shultz KR, Davis JH, Sutherland HJ, Hogge DE, Toze CL, **Klingemann H**. Ex vivo depletion of T-lymphocytes by immunomagnetic beads to decrease graft-versus-host disease after unrelated donor marrow transplantation. American Society of Hematology, 38th Annual Meeting, Dec. 6-10, 1996, Orlando, FL, Blood 1996; 88: 420a.
172. Toze CL, Lim P, Gamage AB, Tomlinson S, Shepherd JD, Nantel SH, Sutherland HJ, Fung HC, **Klingemann HG**, Barnett MJ. Feasibility of patient (Pt) home self-administration of intravenous (IV) ganciclovir (GCV) for cytomegalovirus (CMV) prophylaxis post allogeneic (Allo) bone marrow transplant (BMT): program inception and evaluation. Clin Invest Med 1996; 19 (Suppl. 4): S33.

COPY

173. Toze CL, Reece DE, Wakefield LK, Le A, MacDougall CA, Shepherd JD, Nantel SH, Sutherland HJ, **Klingemann H**, Hogge DE, Barnett MJ. Out-patient antibiotic therapy for leukemia/bone marrow transplant daycare patients: program characterization and evaluation. *Blood* 1996; 99: 302a.
174. Rill DR, Holliday M, Heslop HE, Krance RA, Kimbrough S, **Klingemann H-G**, Brenner MK. Long term Expression by human hemopoietic cells in vivo. *Blood* 1997; 100: 302a.
175. Tam YK, **Klingemann H-G**. Bone marrow transfected with the IL-2 gene for rescuing leukemic relapse following autologous bone marrow transplantation. *Blood* 1997; 100: 302a.
176. Tam YK, Miyagawa B, **Klingemann H-G**. Immunotherapy of malignant melanoma using the natural killer cell line NK-92. *J Hematol* 1998; 7: 277.
177. Hogge D, Eaves C, Barnett MJ, Conneally E, Nantel S, Nevill T, Shepherd J, Sutherland H, Toze C, **Klingemann H-G**. Autologous stem cell transplants cultured in interleukin-2 for high risk acute myelogenous leukemia in first complete remission. American Society of Hematology 40th Annual Meeting, *Blood* 1998; 92: 292a.
178. Lakhani A, Simpson D, Berkahn L, Raptis A, Kaizer H, **Klingemann H-G**. Tandem transplants for stage IV breast cancer: improved results with melphalan for second BMT. American Society of Hematology 40th Annual Meeting, *Blood* 1998; 92: 367b.
179. McCaul K, Nevill TJ, **Klingemann H-G**, Nantel SH, Toze CL, Sutherland HJ, Conneally EA, Shepherd JD, Hogge DE, Currie CJ, Barnett MJ. Treatment of steroid resistant graft-versus-host disease following allogeneic bone marrow transplantation with rabbit anti-thymocyte globulin. American Society of Hematology 37th Annual Meeting *Blood* 1998; 92: 335b.
180. Dracker RA, Sievers E, **Klingemann H-G**. Transplant experience using umbilical cord blood units from a single family cord blood banking service. *Cytotherapy* 1999; 1: 229.
181. Tam Y, **Klingemann H-G**. The natural killer cell line NK-92 for cellular immunotherapy of cancer. *Proceedings of ASCO* 1999; 18: 458a.
182. Hale G, Reece D, Simpson D, Berkahn L, **Klingemann H-G**, Munni R, Nath R, Raptis A, Phillips GL. Intensive therapy with cyclophosphamide, thiotepa and carboplatin and autologous stem cell transplantation for patients with progressive Hodgkin's disease. *Proceedings of ASCO* 1999; 18: 29a.
183. Reece D, Foon K, Ceriani M, Chatterjee M, Connaghan G, Halse G, Holland K, **Klingemann, H-G**, Munn R, Nath R, Teitelbaum A, DiPersio J, Simpson D, Phillips GL. Anti-idiotypic vaccination in conjunction with intensive therapy and autologous stem cell transplantation for patients with metastatic breast cancer. *Proceedings of ASCO* 1999; 18: 124a.
184. Maki G, Tam YK, Berkahn L, **Klingemann H-G**. Ex vivo purging of CML autografts using NK-92 cells. *Blood* 1999; 94: 638a.
185. Tonn T, Esser R, **Klingemann H-G**, Becker S, Bug G, Seidl C, Tam YK, Soerensen J, Loehl U, Bartling T, Hoelzer D, Seifried E, Ottmann O, Schwabe D. Adoptive cellular immunotherapy in advanced cancer using the highly cytotoxic cells line NK-92. *Blood* 1999; 94: 60b.
186. Berkahn LC, Simpson DR, Raptis A, Klunkel L, **Klingemann H-G**. Rituxan in vivo purging prior to collection of stem cells for autologous transplantation in chronic lymphocytic leukemia (CLL). American Society for Blood and Marrow Transplantation 2000 Meeting. *Biol Blood Bone Marrow Transplant* 2000; 6: 137.

COPY

187. Reece DE, Foon K, Chatterjee M, Connaghan DG, Holland HK, Howard D, Munn RK, Nath R, Raptis A, **Klingemann H-G**, Teitelbaum A, Phillips GL. Vaccination with TriAb in conjunction with intensive therapy and autologous stem cell transplantation for patients with metastatic breast cancer. *Proceedings of ASCO* 2000; 19: 101a.
188. Tam YK, Maki G, Berkahn L, **Klingemann H-G**. GMP-compliant, large-scale ex vivo purging of CML PBSC autografts using the natural killer cell line, NK-92. *Cytotherapy* 2000; 2: 315.
189. Tam YK, Doligosa K, Martinson J, Maki G, **Klingemann H-G**. Large-scale expansion of the natural killer cell line, NK-92 under good manufacturing practice conditions for adoptive cellular immunotherapy. *Cytotherapy* 2000; 2: 350.
190. Tam YK, Zou GM, Martinson J, Maki G, Simpson DR, **Klingemann H-G**. Differential effect of CD-40L and TNF-a on maturation of monocyte-derived dendritic cells. *Blood* 2000; 96: 32a.
191. Berkahn LC, Simpson DR, Raptis A, **Klingemann H-G**. Fludarabine/cyclophosphamide/rituxan is an effective regimen for non-myeloablative allogeneic stem cell transplantation for lymphoid malignancies. *Blood* 2000; 96: 352b.
192. Berkahn LC, Simpson DR, Raptis A, Pavletic S, **Klingemann H-G**. Rituxan in vivo purging of stem cells for autologous transplantation in chronic lymphocytic leukemia. *Blood* 2000; 96: 186a.
193. Simpson DR, Berkahn LC, Raptis A, **Klingemann H-G**. Fludarabine/melphalan regimen results in low treatment related mortality and low relapse in myeloma patients undergoing allogeneic stem cell transplant. *Blood* 2000; 96: 409a.
194. Berkahn LC, Simpson DR, Raptis A, **Klingemann H-G**. Fludarabine/cyclophosphamide/Rituxan is an effective regimen for non-myeloablative allogeneic stem cell transplantation for lymphoid malignancies. *Blood* 2000; 96: 352b.
195. Reece DE, Foon KA, Bhattacharya-Chatterjee, Adkins D, Broun ER, Connaghan DG, DiPersio JF, Holland HK, Howard DA, Hale GA, **Klingemann H-G**, Munn RK, Raptis A, Phillips GL. Use of the anti-idiotypic (ID) antibody (AB) vaccine 11D10 (Triab) in patients with metastatic breast cancer undergoing autologous stem cell transplantation. *Blood* 2000; 96: 844a.
196. Raptis A, Mellon-Reppen S, Berkahn L, Simpson D, **Klingemann H-G**. Busulfan, cyclophosphamide (BuCy) and hematopoietic stem cell transplant in myeloid leukemias. *Proceedings of ASCO* 2001; 20: 4b.
197. Miller CB, Waller EK, Anaissie E, Dignani MC, McGuirk J, McSweeney PA, Cagnoni PJ, Fruchtman S, **Klingemann H-G**, Fleck P, Chao N. Reducing nephrotoxicity in hematopoietic progenitor cell transplant recipients: impact of initial versus delayed lipod based amphotericin B treatment. *Blood* 2001; 98: 207a.
198. Rodriguez T, Garcia I, Berkahn L, Arai S, Catchatourian R, Hall M, Myint H, **Klingemann H-G**. Non-myeloablative allogeneic versus in vivo purged autologous blood stem cell transplantation for chronic lymphocytic leukemia. *Blood* 2001; 98: 380b.
199. Rodriguez TE, Simpson D, **Klingemann H-G**. Allogeneic stem cell transplantation utilizing an intensity reduced regimen with fludarabine and melphalan results in low transplant related mortality and low incidence of relapse in multiple myeloma. *Biol Blood Marrow Transplant* 2002; 8: 68.
200. Wels W, Tonn T, Schnierle B, Becker S, **Klingemann H-G**, Uherek C. A NK cell line with a grafted recognition specificity for ErbB2 efficiently kills human cancer cells expressing the ErbB2 proto-oncogene. *Proceedings of AACR* 2002; 43: 968.
201. **Klingemann H-G**. Natural killer based cellular immunotherapy. *Biol Blood Marrow Transplant* 2002; 8: 339.

COPY

202. **Klingemann H-G** Low dose rabbit anti-thymocyte globulin (ATG) in reduced Arai S, Friend P, Myint H, Rich E, Quawi H, Simpson D, intensity conditioning in matched unrelated donor (MUD) transplantation. Blood 2002; 100: 434b.
203. Myint H, Arai S, Rich E, Frind P, Simpson D, **Klingemann H-G** Allogeneic stem cell transplantation from HLA matched sibling donor utilizing reduced intensity regimen consisting of fludarabine and melphalan is safe and effective in patients with advanced myeloma. Blood 2002; 100: 434b.
204. Frame D, **Klingemann H-G**, Myint H, Rich E, Arai S, Hall M, Venugopal V, Devine H, Weinsetin A, Manson S, Drajer D. Decreasing fungal infections in high risk allogeneic stem cell transplant with liposomal amphotericin pre-emptive therapy. Blood 2002; 100: 474b.
205. **Klingemann H-G** Low dose rabbit anti-thymocyte globulin (ATG) in reduced Arai S, Friend P, Myint H, Rich E, Quawi H, Simpson D, intensity conditioning in matched unrelated donor (MUD) transplantation. Blood 2002; 100: 434b.
206. Myint H, Arai S, Rich E, Frind P, Simpson D, **Klingemann H-G** Allogeneic stem cell transplantation from HLA matched sibling donor utilizing reduced intensity regimen consisting of fludarabine and melphalan is safe and effective in patients with advanced myeloma. Blood 2002; 100: 434b.
207. Frame D, **Klingemann H-G**, Myint H, Rich E, Arai S, Hall M, Venugopal V, Devine H, Weinsetin A, Manson S, Drajer D. Decreasing fungal infections in high risk allogeneic stem cell transplant with liposomal amphotericin pre-emptive therapy. Blood 2002; 100: 474b.
208. Arai S, Kindy K, Swearingen M, Meagher R, Friend P, Maki G, Martinson J, Myint H, **Klingemann H-G**. Phase I study of adoptive immunotherapy using the cytotoxic natural killer (NK) cell line, NK-92, for treatment of advanced renal cell carcinoma and malignant melanoma. Blood 2003; 102: 693a.
209. Kroger N, Perez-Simon J, Myint H, **Klingemann H-G**, Shimoni A, Tomas J, Schwerdtfeger R, Kiehl M, Fauser A, Sayer HG, de Leon A, Beyer J, Zabelina T, Ayuk F, Miguel JS, Brand R, Zander A. Influence of timing allogeneic stem cell transplantation after dose-reduced melphalan/fludarabine conditioning in multiple myeloma. Blood 2003; 102: 728a.
210. Kroger N, Schilling G, Einsele H, Miguel PS, Kiehl M, Fauser A, Schwerdtfeger R, Wandt H, Sayer HG, Myint H, **Klingemann H-G**, Hinke A, Zander A. Deletion of chromosome 13q14 detected by fluorescence in situ hybridization as prognostic factor following allogeneic dose-reduced stem cell transplantation in patients with multiple myeloma. Blood 2003; 102: 729a.
211. Hayes G, Friend P, **Klingemann H-G**. Polymorphism in IgG Fc receptor FcγRIIIA gene in allogeneic bone marrow transplant recipients. Blood 2003; 102: 395b.
212. Bae J, Martinson JA, **Klingemann H-G**, Treon S, Anderson KC, Munshi NC. Induction of multiple myeloma specific cytotoxic T lymphocytes using HLA-A2.1 specific CD19 and CD20 peptides. Blood 2004; 104: 679a.
213. Romanski A, Krzossok N, Uherek C, Bug G, Rossig C, Kampfmann M, Hoelzer D, Seifried E, **Klingemann H-G**, Wels W, Ottmann O, Tonn T. Retargeting of a NK cell line (NK-92) with specificity for CD19 efficiently kills human B-precursor leukemia cells. Cytotherapy 7 (Suppl 1): 137, 2005
214. Newton B, Sprague K, Klein A, **Klingemann HG**, Chan G. Single antigen mismatched related donor allogeneic stem transplants have similar outcomes as matched unrelated donor allogeneic stem cell transplants: A single center's experience. Blood 2005; 106: 583a

COPY

215. Delcommenne M, **Klingemann H-G**, Gregory S. A novel anti CD23 fully human monoclonal antibody potentially useful for B-CLL Therapy. Blood 2005; 106: 343b
216. Sprague K, Padagaonkar V, Klein A, Chan, G, Miller K, **Klingemann, H**. Mitoxantrone and melphalan conditioning regimen for autologous peripheral blood stem cell transplantation in adults with acute myelogenous leukemia. Blood 2005; 106: 466b
217. Tuncer H, Betancur M, Boissel L, Friedman R, **Klingemann H**. Ex vivo expansion and mRNA transfection of cord blood derived natural killer cells with preserved cytotoxicity. Blood 108: 1045a, 2006
218. Friedman R, Betancur M, Tuncer M, Boissel L, Cetrulo C, **Klingemann H**. Co-transplantation of autologous umbilical cord matrix mesenchymal stem cells improves engraftment of umbilical cord in NOD/SCID mice. Blood 108:726a, 2006
219. Boissel L, Betancur M, Tuncer H, Weitzman J, **Klingemann H**. Transfection with CD19 specific chimeric antigen receptor restores natural killer cell mediated killing of CLL cells. Blood 110: 915 A, 2007
220. Weitzman J, Betancur M, Boissel L, Rabinowitz AP, **Klingemann H**. Variable contribution of different monoclonal antibodies to NK cell mediated ADCC against primary CLL cells. Blood 110:252 B, 2007

*U.S. Patent Appn. Serial No. 10/008,955
Declaration of Hans Klingemann, M.D., Ph.D.
Filed in conjunction with Response to Final Office Action
filed on October 15, 2008*

COPY

EXHIBIT 2

NK-92 phase I trial

Infusion of the allogeneic cell line NK-92 in patients with advanced renal cell cancer or melanoma: a phase I trial

S Arai, R Meagher, M Swearingen, H Myint, E Rich, J Martinson and H Klingemann

Rush University Medical Center, Chicago, Illinois, USA

Background

Renal cell cancer and malignant melanoma are two types of cancer that are responsive to immunotherapy. In this phase I dose-escalation study, the feasibility of large-scale expansion and safety of administering ex vivo-expanded NK-92 cells as allogeneic cellular immunotherapy in patients with refractory renal cell cancer and melanoma were determined.

Methods

Twelve patients (aged 31–74 years) were enrolled, three per cohort at cell dose levels of $1 \times 10^8/\text{m}^2$, $3 \times 10^8/\text{m}^2$, $1 \times 10^9/\text{m}^2$ and $3 \times 10^9/\text{m}^2$. One treatment course consisted of three infusions. Eleven patients had refractory metastatic renal cell cancer; one patient had refractory metastatic melanoma.

Results

The NK-92 cells were expanded in X-Vivo 10 serum-free media supplemented with 500 U/mL Proleukin recombinant human

interleukin-2 (rhIL-2), amino acids and 2.5% human AB plasma. Final yields of approximately 1×10^9 cells/culture bag ($218\text{--}250 \times$ expansion) over 15–17 days were achievable with $\geq 80\%$ viability. Infusional toxicities of NK-92 were generally mild, with only one grade 3 fever and one grade 4 hypoglycemic episode. All toxicities were transient, resolved and did not require discontinuation of treatment. One patient was alive with disease at 4 years post-NK-92 infusion. The one metastatic melanoma patient had a minor response during the study period. One other patient exhibited a mixed response.

Discussion

This study establishes the feasibility of large-scale expansion and safety of administering NK-92 cells as allogeneic cellular immunotherapy in advanced cancer patients and serves as a platform for future study of this novel natural killer (NK)-cell based therapy.

Keywords

cancer, cell therapy, NK-92, phase I.

Introduction

Treatment options remain very limited for patients with metastatic renal cancer and metastatic melanoma. Median survival is 7–10 months for metastatic renal cancer and metastatic melanoma and both diseases are resistant to chemotherapy and/or radiotherapy [1]. Both cancers, however, seem to be responsive to immunotherapy [2–4] and cellular immunotherapy is increasingly being considered as a form of treatment that is non-cross-reactive with prior chemotherapy and radiation [5,6].

Natural killer (NK) cells are particularly attractive for adoptive cellular immunotherapy because of their unique ability to lyse target cells without priming [7]. Autologous

NK cells from cancer patients, however, may be dysfunctional and may not recognize the malignant target. Autologous NK cells may also be inhibited by 'self' HLA expression and some tumors may in fact express functional HLA antigens (Ag) capable of inhibiting NK cell function. Allogeneic NK cells, therefore, potentially represent a better NK cell product for immunotherapy. NK-92 is a human NK-cytotoxic cell line that represents a pure allogeneic activated NK cell source. NK-92 is interleukin-2 (IL-2) dependent, lacks killer cell inhibitory receptors (KIR) and is broadly cytotoxic against a variety of hematologic and solid tumor cell lines, including leukemia, lymphoma, malignant melanoma, prostate cancer and

breast cancer [8]. *Ex vivo* expansion of NK-92 under good tissue practice (GTP) conditions for clinical use has allowed its entry into phase I study as a novel immunotherapy in advanced cancers [9]. The NK-92 cell line is originally derived from a non-Hodgkin's lymphoma with large granular lymphocyte morphology and a CD56⁺CD3⁺CD16⁺ immunophenotype. Studies in SCID mice have confirmed that NK-92 inoculation itself is not leukemogenic. The tumoricidal activity of NK-92 against human leukemias has been tested *in vitro* against leukemic cell lines and primary leukemia cells, as well as *in vivo* by adoptive transfer of NK-92 cells into xenografted SCID mice, with the result of prolonged survival and no signs of leukemia development [10]. NK-92 infusion has further been found to prolong survival in SCID mice inoculated with human malignant melanoma cells, an observation that served as the basis for this clinical trial [11].

The objective of this study was to determine the safety of infusing NK-92 cells in patients with advanced renal cell cancer and melanoma. The three infusions, each given 48 h apart, had no severe side-effects and several patients showed objective anti-tumor responses, suggesting further exploration of this cellular treatment modality in selected cancer indications is warranted.

Methods

Patient eligibility

The study was open from April 2002 to June 2004 at Rush University Medical Center (Chicago, IL, USA). The protocol was approved by the Institutional Review Board and had obtained FDA investigational new drug application status for the *ex vivo* expansion of NK-92 cells. All patients signed informed consent before any study-related procedures. Patients with histologically confirmed metastatic renal cell cancer or malignant melanoma refractory to, or having failed, standard therapy, including surgery, radiation and chemotherapy, were eligible for treatment on this protocol. All patients had measurable disease [by computed tomography (CT) scan or physical examination] and had undergone several prior treatments, including high-dose IL-2 therapy and allogeneic stem cell transplant (SCT). Other eligibility criteria included ECOG 0 or 1, white blood cells (WBC) $>2.0 \times 10^9/L$, Hb >8 g/dl, platelets $\geq 75 \times 10^9/L$, creatinine <2.0 mg/dL and total bilirubin <2.0 mg/dL. Exclusion criteria included ECOG ≥ 2 and concurrent treatment with corticosteroids and/or other immunosuppressive drugs.

Trial design

The trial was a single-center, open-label, dose-escalation study. Three patients were treated at each dose level: 1×10^8 cells/m², 3×10^8 cells/m², 1×10^9 cells/m² and 3×10^9 cells/m². One treatment course consisted of three infusions of the cell dose over 48 h. Infusion days were designated as days 1, 3 and 5. The rationale for the schedule was to infuse as many NK-92 cells before a T-cell directed immune response would theoretically occur.

Manufacturing of the NK-92 cell product

Manufacturing of clinical-grade NK-92 cells was performed under GTP conditions at the Sramek Center for Cell Engineering at Rush University Medical Center [9]. At 3 weeks before the targeted date of infusion, NK-92 cell cultures were initiated from the NK-92 Working Cell Bank. NK-92 cells were expanded in X-Vivo 10 serum-free medium supplemented with 500 U/mL Proleukin recombinant human (rh)IL-2, 0.6 mm l-asparagine, 3 mm l-glutamine, 1.8 mm l-serine and 2.5% human AB plasma. The cultures were initiated at 2.5×10^5 cells/mL in 25 mL (6.25×10^6 cells) in 1-L Vuelife culture bags (American Fluoroseal Corp., Gaithersburg, MD, USA), with the addition of media every 3 days, maintaining a density of 2.5×10^5 cells/mL, and with daily mild disruption of cell aggregates. Final yields of approximately 1×10^9 cells/culture bag (218–250-fold expansion) over 15–17 days was achievable, with $\geq 80\%$ viability. After quality control verification and quality assurance release that included Gram stain, culture and mycoplasma testing, the final NK-92 cell product was resuspended in GM-2 medium (Plasma-Lyte-A medium supplemented with 2.5% human AB plasma) and infused fresh. The last feeding with rhIL-2 and fresh medium was 48 h before the first day of infusion of the expanded NK-92 product. In addition, after completion of the cell culture period, a standard cytotoxicity assay was performed to assess the functional capacity of the *ex-vivo*-expanded NK-92 cells. Calcein AM-labeled K562 and Raji cells were used as targets to determine NK-92 cell cytotoxicity of the *ex vivo*-expanded cells. The NK-92 cells were irradiated with 1000 cGy prior to infusion into the patient (Cesium Source-Blood Bank, Rush University Medical Center).

On the day of infusion, hydration (200 mL NS/h) was given to the patient 2 h prior to the NK-92 cell infusion and continued for 2 h after NK-92 infusion. The total volume of the NK-92 cell product infusate was

100–200 mL, depending on the body weight of the individual patient. The cells were infused at a rate of 5 mL/min, with a total infusion time of approximately 20–30 min. All patients received premedication with diphenhydramine before the start of each cell infusion.

Of note, the NK-92 cell line was being commercialized during the course of the clinical trial.

Treatment and follow-up

Complete tumor staging was performed prior to NK-92 treatment. During cell infusion, patients were closely monitored, with vital signs recorded at 0, 15, 30, 60, 90, 120 and 240 min and every 24 h thereafter. Patients were examined daily for clinical toxicity from NK-92 infusion for the first 7 days and then weekly thereafter until 4 weeks after cell infusion. NCI-CTC version 3 criteria were used to document toxicities. CBC and chemistries were performed daily during the treatment course. CT scans were repeated at 2 and 4 weeks after the treatment course to assess disease response, and thereafter per routine by their local oncologist. Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) [12]. Additionally, a minor response was defined as regression of target tumor lesions by 10–30% with no new lesions and no non-target lesion progression. A mixed response was defined as the regression of some lesions but simultaneous progression of others.

Cytokine assays

Patient sera were collected pre-NK-92 cell infusion (time 0), at 4 h after each infusion on days 1, 3 and 5, and at 7 days post-infusion. The sera at each time point were tested by enzyme-linked immunosorbent assay (ELISA) with a standard multiplexed panel of cytokines (Linco Diagnostic Services Inc., St Charles, MI, USA). The cytokine panel consisted of IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, interferon (IFN)- γ , granulocyte-macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor (TNF)- α . Four patients had cytokines measured at the higher NK-92 dose level with the hypothesis that the higher cell dose of NK-92 would tend to be more effective.

HLA antibody production

High-resolution DNA typing of the NK-92 cell line was used to establish its HLA type. High-resolution DNA typing for HLA was also performed on two patients for

whom 1–2 year follow-up blood samples were available. The patient HLA class I and class II antibody (Ab) production against NK-92 was determined for these samples using standard cytotoxic cross-match and flow cytometric cross-match testing.

Statistical analysis

Analyzes were descriptive and graphical. Under the cytokine analysis, a one-sided sign-test was applied to the data from the four patients who had cytokines measured, to test the significance of the average of pre-post differences.

Results

Patient characteristics

The characteristics of the 12 patients enrolled in the study are summarized in Table 1. The median age was 50 years (range 31–74 years); eight patients were male and four were female. Eleven patients had refractory metastatic renal cell cancer, predominantly clear cell type. One patient had refractory metastatic melanoma, spindle cell type. Prior therapies included nephrectomy, high-dose IL-2, IFN, radiation, chemotherapy and SCT.

Table 1. Baseline characteristics of patients treated with NK-92 ($n = 12$)

Variable	Summary
Median age (years)	50 (range 31–74)
Gender	
Male	8
Female	4
Type of tumor	
Renal cell carcinoma	11
Melanoma	1
Metastatic sites	
Lung	10
Liver	4
Brain/central nervous system	1
Bone	3
Lymph nodes	6
Other	2
Prior therapies	
Surgery	11
IL-2, other immunotherapy (IFN, thalidomide)	10
Chemotherapy	3
Stem cell transplant	1
Radiation	4
Vaccine	1

Toxicity

All 12 patients received the three infusions of NK-92 per protocol and there were no delays in the infusion days. Table 2 summarizes the NK-92-related toxicities during the treatment course. Three patients (patients 8, 9 and 12) experienced grade 1 fevers (range 38.2–38.7°C) during the course of NK-92 infusion and all occurred with the higher dose level of $1 \times 10^9/\text{m}^2$. The fevers were self-limited and did not require treatment. The patient with metastatic melanoma developed a temperature of 41°C 4 h after the third infusion of NK-92, which responded to hydrocortisone 100 mg intravenously (i.v.). Blood and urine cultures, as well as culture of the NK-92 bag, were negative. This patient had new onset softening of his bulky pre-auricular and occipital tumor masses with frank drainage from the pre-auricular mass as it softened. There were no serious infections reported for patients at the 1-year follow-up post-NK-92 infusion.

Toxicities that were attributed to the underlying tumor and unrelated to NK-92 infusion included grade 2 neck and chest pains and grade 3 back pain in a patient with bulky retroperitoneal renal cell cancer. One grade 4 hypoglycemic episode (glucose < 20 mg/dL) with symptoms of confusion and seizure-like activity occurred immediately after the first NK-92 infusion in a non-diabetic patient (11) who had extensive liver metastases. The patient's baseline glucose was normal at 162 mg/dL. The hypoglycemia responded to D50 bolus followed by continuous D5 i.v. infusion overnight. No further hypoglycemia episodes occurred with the subsequent two NK-92 infusions.

Clinical outcomes

The follow-up on this study is now 4 years, with all patients followed until death. Patients were allowed to seek other therapies after the 4-week toxicity monitoring period. As a phase I study, the study was not designed to evaluate formally the tumor response or duration of response. One patient (6) had a transient mixed response during the monitoring period. She had extensive metastases in the bilateral lungs, hila, mediastinum, abdominal and retroperitoneal nodes. The mixed response occurred as progression in the mediastinum but reduction in lung masses. She ultimately progressed and died at day 168 post-treatment. Patient 10, with melanoma, had a minor response in a target lesion at the left upper neck that was documented at 2 weeks post-infusion by physical examination and CT scan (Figure 1a,b). This patient, with very advanced disease, subsequently progressed and received alternative therapy, but did survive to 255 days post-NK-92 therapy. Of the 12 patients who completed NK-92 treatment, 11 have subsequently died, 10 from progressive disease. Patient 3, who underwent reduced-intensity allogeneic sibling-matched transplant subsequent to NK-92 treatment, died 2.5 years later from consequences of the post-transplant immunosuppressed state, with bronchopneumonia and no active renal cell cancer. Patient 7 is the only surviving patient post-NK-92 infusion. He had progression at 4 weeks post-NK-92 infusion and went on to receive salvage therapies as allowed by the protocol. He was alive with disease and seeking further therapy for renal

Table 2. Adverse events in patients receiving NK-92 infusions. The severity of adverse events was graded according to NCI-CTC version 3

Subject	Diagnosis	Cell dose/ $\text{m}^2 \times 3$ doses	Adverse event w/grade (possibly related)
1	RCC	1×10^8	0
2	RCC	1×10^8	0
3	RCC	1×10^8	0
4	RCC	3×10^8	0
5	RCC	3×10^8	0
6	RCC	3×10^8	0
7	RCC	1×10^9	0
8	RCC	1×10^9	1, fever
9	RCC	1×10^9	1, fever
10	Melanoma	3×10^9	3, fever
11	RCC	3×10^9	4, hypoglycemia
12	RCC	3×10^9	1, fever

RCC, renal cell cancer.

Table 3. Clinical outcomes

Subject	Diagnosis	Cell dose/m ² × 3 doses	Outcome at 4 weeks	Deaths (unrelated to NK-92)
1	RCC	1 × 10 ⁸	PD*	D1006, PD
2	RCC	1 × 10 ⁸	PD	D101, PD
3	RCC	1 × 10 ⁸	PD†	D832, bronchopneumonia
4	RCC	3 × 10 ⁸	PD	D666, PD
5	RCC	3 × 10 ⁸	PD	D188, PD
6	RCC	3 × 10 ⁸	Mixed	D168, PD
7	RCC	1 × 10 ⁹	PD	Alive D1450
8	RCC	1 × 10 ⁹	SD	D212, PD
9	RCC	1 × 10 ⁹	SD†	D1059, PD
10	Melanoma	3 × 10 ⁹	MR	D255, PD
11	RCC	3 × 10 ⁹	SD	D695, PD
12	RCC	3 × 10 ⁹	SD	D466, PD

RCC, renal cell cancer; PD, progressive disease; SD, stable disease; MR, minor response; D, day. *prior alloSCT; †subsequent alloSCT.

cell cancer at the latest follow-up, on day 1450 post-NK-92.

Laboratory findings

There was a trend of LDH elevations that occurred with NK-92 infusion at the higher cell dose level of $1 \times 10^9/\text{m}^2$ (Figure 2). Patient 8 went from a baseline LDH of 185 U/L to 1269 U/L (normal 200–650 U/L) after the first NK-92 infusion, peaked at 2157 U/L after the third infusion, and remained elevated through day 7 (1493 U/L). Patient 11,

with the hypoglycemic episode, had a dramatic increase in her serum LDH to 1219 U/L at 4 h after the first NK-92 infusion. The LDH remained elevated through the subsequent two infusions, 1536 and 1254 U/L, respectively, but normalized at day 14 of the treatment course to 237 U/L. Patient 10, with metastatic melanoma, who developed high-grade fever and a clinical tumor response, similarly had elevation from a baseline normal LDH of 409 U/L to a peak of 791 U/L and 763 U/L on infusion days 3 and 5, respectively, with ultimate normalization to 327 U/L at day 14.

Other laboratory parameters examined did not show clinically significant changes in total WBC, platelets, neutrophil count, lymphocyte count or eosinophil count in patients over the three NK-92 infusions or in the 4 weeks of follow-up.

Cytokines were measured in four of the higher cell dose patients' sera pre-, at 4 h post- each of the three NK-92

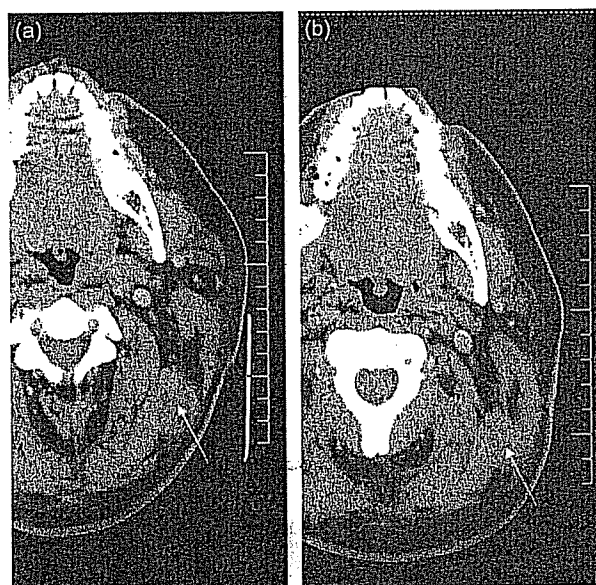


Figure 1. (a) Patient 10, pre-NK-92 infusion, left upper neck mass, 3.15×2.54 cm. (b) Two weeks post-NK-92 infusion, shrinkage of left upper neck mass, 2.46×1.76 cm.

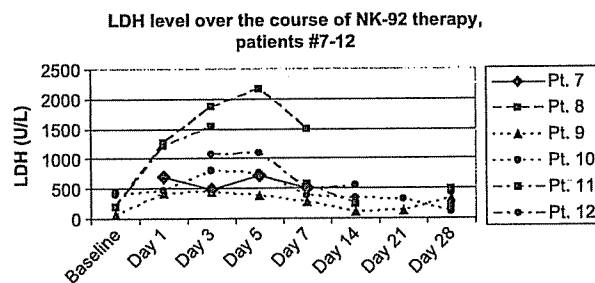


Figure 2. Trend of LDH elevation during NK-92 infusion starting at $1 \times 10^9/\text{m}^2$ cell dose. After an initial increase during treatment, the LDH values return to baseline by day 14.

infusions, and at 7 days post-infusion. Positive elevations in IL-6, IL-8 and IL-10 cytokines were seen with NK-92 infusion at the higher cell doses, perhaps suggesting tumor lysis. In patient 10, with metastatic melanoma, clinical tumor shrinkage correlated with a massive rise in IL-6, to 6819 pg/mL from a baseline of 17 pg/mL, along with grade 3 fever. IL-8 and IL-10 similarly rose (Table 4) and then normalized by day 7 post-infusion. Another observation was in patient 9, with metastatic renal cell cancer, who had baseline elevations of IL-4, IL-6 and IL-8, possibly reflecting constitutive cytokine secretion from the renal tumor.

As only four patients had cytokines measured, the sample size limited the degree of statistical reliability. However, if the IL-6, IL-8 and IL-10 pre-post differences (three per patient) are averaged within patients, in all four patients the average pre-post difference was always positive. This has a one-sided sign-test *P*-value of 0.0625, which is the smallest *P*-value obtainable in a non-parametric test with only four patients.

High-resolution HLA typing for NK-92 was confirmed as follows: A3, A11; B7, B44, Bw4⁺, Bw6⁺; Cw*07(3R), Cw*1601(3R); DR7, DR15; DQ2, DQ6; DR51⁺, DR52⁻, DR53⁺. Samples from two patients (1 and 11) were tested for the development of anti-HLA Ab against NK-92. Patient 1 was found to have both HLA class I and class II

Ab to the NK-92 cell line at 2 years post-exposure. Cytotoxicity and flow cytometric cross-match assays were also positive for this patient. For patient 11, panel reactive Ab and cross-match assays were negative at 1 year post-exposure.

Discussion

The development of the continuously growing NK-92 as a universal donor of highly cytotoxic tumoricidal cells is attractive for allogeneic cellular immunotherapy. Renal cell cancer and melanoma were chosen as the target diseases for this trial based on their previously reported immune responsiveness as tumors [2-4].

The main objective of the phase I trial was to determine the feasibility and safety of administration of NK-92 cell therapy with multiple infusions in these advanced cancer patients. NK-92 cells were successfully expanded under GTP conditions, on average 200-fold over 15-17 days with $\geq 80\%$ viability. Infusional toxicities were generally minimal, limited to grade 1 fevers. No severe hemodynamic or hematologic toxicities were seen with the NK-92 infusion, and thus it compares favorably with other cellular immunotherapies that have used autologous NK or allogeneic haplo-identical NK cells [13-18].

The two major toxicities of grade 3 fever and grade 4 hypoglycemia seen in two patients, while temporally

Table 4. Serum cytokine measurements pre- and post-NK-92 doses. Cytokines were measured in the patients' sera before, 4 post- each of the three NK-92 infusions and at 7 days post-NK-92 infusion. Elevations in IL-6, IL-8 and IL-10 cytokines were seen with NK-92 infusion in the sample of four patients at the higher cell doses, with return to baseline by day 7

Patient	Diagnosis	Cell dose/ m ² × 3 doses	NK-92 infusion no.	IL-6* (pg/mL)			IL-8* (pg/mL)			IL-10* (pg/mL)		
				Pre-	Post-	Day 7	Pre-	Post-	Day 7	Pre-	Post-	Day 7
8	RCC	1 × 10 ⁹	1	34	71		5	15		< 3	< 3	
			2	215	94		11	6		< 3	4	
			3	125	214	35	9	12	10	< 3	< 3	< 3
9	RCC	1 × 10 ⁹	1	282	307		339	298		41	22	
			2	291	276		257	327		7	74	
			3	284	286	282	299	309	305	7	24	9
10	Melanoma	3 × 10 ⁹	1	17	18		20	24		< 3	< 3	
			2	46	29		27	19		66	44	
			3	17	6819	14	20	607	15	< 3	159	< 3
11	RCC	3 × 10 ⁹	1	4	13		25	37		42	906	
			2	< 3	< 3		15	19		32	327	
			3	< 3	< 3	< 3	16	21	31	19	190	96

*The one-sided sign test has a *P*-value of 0.0625 for the average of pre-post differences.

related to the NK-92 infusions, could be reflective of tumor lysis responses in these large tumor burden patients versus a reaction to the infusion of cells. The hypoglycemic response in patient 11, who had extensive liver metastases, could be related to tumor-induced hypoglycemia, which has been described in patients with extensive liver metastases [19]. Such a response could be the result of the release of insulin or a humoral hypoglycemic factor, such as an insulin-like substance or diminished glycogen stores in the liver from extensive metastases [19], or ectopic hormone production by the primary renal tumor, such as IGF-2, that can cause hypoglycemia [20]. Hypoglycemia in this setting might also be interpreted as a surrogate for a tumor lysis reaction [21], as may the increase in LDH seen in several patients after infusion of NK-92. LDH increase is rather non-specific, however, and one cannot rule out other possibilities for the rise in LDH, such as from dead or dying NK-92 cells that were irradiated prior to infusion.

Similarly, elevations in IL-6, IL-8 and IL-10 with NK-92 infusion at the higher cell doses might suggest tumor lysis reaction. However, the cancers themselves can express these cytokines, as can the NK-92 cell line or a toxic response to the infusion of the cells, making it difficult to interpret the cytokine responses in a small sample of patients.

One patient developed HLA Ab whereas another did not. This result may point to a variability in the immune response to NK-92, and this may in part be explained by the variable host immunocompromised status. Other factors to consider are that prior blood product transfusions in the patient could induce an alloimmune response that is cross-reactive with those Ag expressed by NK-92. A larger number of patients will need to be studied to answer this issue. Still, there would seem to be a logical approach in avoiding retreatment of patients having a positive cross-match beyond a 7-day window in order to prevent an anamnestic response.

The exact mechanism of NK-92 killing has not been established; however, it can be hypothesized that NK-92 essentially lacks KIR because of its immature status, and thus target killing is predominantly through its natural cytotoxicity receptors (NKp30 and NKp46) and activating receptor NKG2D [22], rather than a KIR-mediated NK alloreactivity mechanism. The clinical advantage may be that allogeneic NK cellular therapy with NK-92 has a broader spectrum of tumor killing because it overcomes

the 'self' MHC molecule restriction, much as has been hypothesized for adoptive transfer of haplo-identical NK cells in patients with cancer [18,23].

Efficacy was not determined in this phase I trial; however, there were two patients with changes in tumor measurement that seemed to meet minor and mixed responses during the study period. These changes were, as expected, transient in this heavily pretreated population. Having determined the safety of infusion and feasibility of large-scale expansion in this initial study, the future plans with NK-92 include a phase II study to determine the biologic activity in other advanced cancers, and to draw on its unique advantage as a cell line to be a platform for genetic engineering to target tumor Ag, such as ErbB2 [24] and CD20 [25], to increase the potential for improved tumor localization and killing efficacy.

Acknowledgements

We thank the nurse practitioners, Kelly Kindy, Patricia Friend and Christina Havey, and staff of 10 Kellogg at Rush University Medical Center, Chicago, IL, for their help in co-ordination of patient care and data collection; Guitta Maki for NK-92 laboratory support; Michele Prod for technical HLA laboratory support, and Philip Lavori at Stanford for statistical consultation.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

- 1 DeVita Jr VT, Hellman S, Rosenberg SA. *Cancer: Principles & Practice of Oncology*, 7th edition. Philadelphia: Lippincott Williams and Wilkins, 2004.
- 2 Rosenberg SA, Yang JC, Topalian SL *et al.* Treatment of 283 consecutive patients with metastatic melanoma or renal cell cancer using high-dose bolus interleukin 2. *JAMA* 1994;271: 907-13.
- 3 Rosenberg SA, Yang JC, White DE, Steinberg SM. Durability of complete responses in patients with metastatic cancer treated with high-dose interleukin-2: identification of the antigen-mediated response. *Ann Surg* 1998;228:307-19.
- 4 Fisher RI, Rosenberg SA, Fyfe G. Long-term survival update for high-dose recombinant interleukin-2 in patients with renal cell carcinoma. *Cancer J Sci Am* 2000;6(Suppl 1):S55-7.
- 5 Thompson JA, Figlin RA, Sifri-Steele C *et al.* A phase I trial of CD3/CD28-activated T cells (Xcellerated T cells) and interleukin-2 in patients with metastatic renal cell carcinoma. *Clin Cancer Res* 2003;9:3562-70.

- 6 Visonneau S, Cesano A, Porter DL *et al*. Phase I trial of TALL-104 cells in patients with refractory metastatic breast cancer. *Clin Cancer Res* 2000;6:1744–54.
- 7 Miller J. The biology of natural killer cells in cancer, infection, and pregnancy. *Exp Hematol* 2001;29:1157–68.
- 8 Tonn T, Becker S, Esser R *et al*. Cellular immunotherapy of malignancies using the clonal natural killer cell line NK-92. *J Hematother Stem Cell Res* 2001;10:535–44.
- 9 Tam YK, Martinson JA, Doligosa K, Klingemann H-G. *Ex vivo* expansion of the highly cytotoxic human natural killer cell line NK-92 under current good manufacturing practice conditions for clinical adoptive cellular immunotherapy. *Cytotherapy* 2003;5:259–72.
- 10 Yan Y, Steinhert P, Klingemann H-G *et al*. Antileukemia activity of a natural killer cell line against human leukemias. *Clin Cancer Res* 1998;4:2859–68.
- 11 Tam YK, Miyagawa B, Ho VC, Klingemann HG. Immunotherapy of malignant melanoma in a SCID mouse model using the highly cytotoxic natural killer cell line NK-92. *J Hematother* 1999;8:281–90.
- 12 Therasse P, Arbuck SG, Eisenhauer EA *et al*. New guidelines to evaluate the response to treatment in solid tumours: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16.
- 13 Rosenberg SA, Lotz MT, Muul LM *et al*. Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. *N Eng J Med* 1985;313:1485–92.
- 14 Benyunes MC, Massumoto C, York A *et al*. Interleukin-2 with or without lymphokine-activated killer cell as consolidative immunotherapy after autologous bone marrow transplantation for acute myelogenous leukemia. *Bone Marrow Transplant* 1993;12:159–63.
- 15 Rosenberg SA, Lotz MT, Yang JC *et al*. Prospective randomized trial of high-dose interleukin-2 alone or in conjunction with lymphokine-activated killer cells for the treatment of patients with advanced cancer. *J Natl Cancer Inst* 1993;85:622–32.
- 16 Velardi A, Ruggeri L, Moretta A, Moretta L. NK cells: a lesson from mismatched hematopoietic transplantation. *Trends Immunol* 2002;23:438–44.
- 17 Passweg JR, Tichelli A, Meyer-Monard S *et al*. Purified donor NK-lymphocyte infusion to consolidate engraftment after haploidentical stem cell transplantation. *Leukemia* 2004;18:1835–8.
- 18 Miller JS, Soignier Y, Panoskaltis-Mortari A *et al*. Successful adoptive transfer and in vivo expansion of human haploidentical NK cells in patients with cancer. *Blood* 2005;105:3051–7.
- 19 Hoff AO, Vassilopoulou-Sellin R. The role of glucagon administration in the diagnosis and treatment of patients with tumor hypoglycemia. *Cancer* 1998;82:1585–92.
- 20 Berman J, Harland S. Hypoglycemia caused by secretion of insulin-like growth factor 2 in a primary renal cell carcinoma. *Clin Oncol (R Coll Radiol)* 2001;13:367–9.
- 21 Silverman P, Distelhorst CW. Metabolic emergencies in clinical oncology. *Semin Oncol* 1989;16:504–15.
- 22 Moretta L, Bottino C, Pende D *et al*. Human natural killer cells: molecular mechanisms controlling NK cell activation and tumor cell lysis. *Immunol Lett* 2005;100:7–13.
- 23 Ruggeri L, Capanni M, Urbani E *et al*. Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. *Science* 2002;295:2097–100.
- 24 Uherek C, Tonn T, Uherek B *et al*. Retargeting of natural killer-cell cytolytic activity to ErbB2-expressing cancer cells results in efficient and selective tumor cell destruction. *Blood* 2002;100:1265–73.
- 25 Mueller T, Uherek C, Maki G *et al*. Expression of a CD20-specific antigen receptor enhances activity of NK cells and overcomes NK-resistance of lymphoma and leukemia cells. *Cancer Immunol Immunother*, in press.

Acknowledgement Receipt

The USPTO has received your submission at **13:44:00** Eastern Time on **15-OCT-2008** by Deposit Account: 032026.

\$ **960** fee paid by e-Filer via RAM with Confirmation Number: 8657.

You have also pre-authorized the following payments from your USPTO Deposit Account:







Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

eFiled Application Information

EFS ID	4117342
Application Number	10008955
Confirmation Number	5420
Title	Natural killer cell lines and methods of use
First Named Inventor	Hans Klingemann
Customer Number or Correspondence Address	30058
Filed By	Christine W. Trebilcock/Dennis Ditzenberger
Attorney Docket Number	06-129 PCT/US/CIP
Filing Date	07-DEC-2001
Receipt Date	15-OCT-2008
Application Type	Utility under 35 USC 111(a)

COPY**Application Details**

Submitted Files	Page Count	Document Description	File Size	Warnings
06-129-RCE.pdf	3	Request for Continued Examination (RCE)	316578 bytes	 WARNINGS
This is not a USPTO supplied RCE SB30 form.				
06-129-Response.pdf	13	Amendment Submitted/Entered with Filing of CPA/RCE	1070665 bytes	 PASS
06-129-Rule-132-Declaration.pdf	54	Rule 130, 131 or 132 Affidavits	6222181 bytes	 PASS
06-129-Submission.pdf	5	Miscellaneous Incoming Letter	212526 bytes	 PASS
06-129-PCT-US-CIP-Sequence.txt	-	Sequence Listing (Text File)	810 bytes	 PASS
fee-info.pdf	2	Fee Worksheet (PTO-06)	32351 bytes	 PASS

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt

similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

COPY

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

If you need help:

- *Call the Patent Electronic Business Center at (866) 217-9197 (toll free) or e-mail EBC@uspto.gov for specific questions about Patent e-Filing.*
- *Send general questions about USPTO programs to the [USPTO Contact Center \(UCC\)](#).*
- *If you experience technical difficulties or problems with this application, please report them via e-mail to [Electronic Business Support](#) or call 1 800-786-9199.*

Electronic Acknowledgement Receipt

EFS ID:	4117342
Application Number:	10008955
International Application Number:	
Confirmation Number:	5420
Title of Invention:	<div>COPY</div> Natural killer cell lines and methods of use
First Named Inventor/Applicant Name:	Hans Klingemann
Customer Number:	30058
Filer:	Christine W. Trebilcock/Dennis Ditzenberger
Filer Authorized By:	Christine W. Trebilcock
Attorney Docket Number:	06-129 PCT/US/CIP
Receipt Date:	15-OCT-2008
Filing Date:	07-DEC-2001
Time Stamp:	13:44:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$960
RAM confirmation Number	8657
Deposit Account	032026
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees,

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	06-129-RCE.pdf	316578 ef56527dc547dfe955b2a1006201a30e52bd4ce8	no	3

Warnings:

This is not a USPTO supplied RCE SB30 form.

COPY

Information:

2	Amendment Submitted/Entered with Filing of CPA/RCE	06-129-Response.pdf	1070665 d67e4d3f6e5d72b33c0aad503fc791a67c103b3	no	13
---	--	---------------------	--	----	----

Warnings:

Information:

3	Rule 130, 131 or 132 Affidavits	06-129-Rule-132-Declaration.pdf	6222181 2250cc75b9622366202f65c3d2a8fb987ebd7256	no	54
---	---------------------------------	---------------------------------	---	----	----

Warnings:

Information:

4	Miscellaneous Incoming Letter	06-129-Submission.pdf	212526 e80915a3d5b67c11d80d5285d0fc2d87ae610dd	no	5
---	-------------------------------	-----------------------	---	----	---

Warnings:

Information:

5	Sequence Listing (Text File)	06-129-PCT-US-CIP-Sequence.txt	810	no	0
---	------------------------------	--------------------------------	-----	----	---

Warnings:

Information:

6	Fee Worksheet (PTO-06)	fee-info.pdf	32351 91aa229d2ebdf49f15b5002d5ea1181771d7f082	no	2
---	------------------------	--------------	---	----	---

Warnings:

Information:

Total Files Size (in bytes):

7855111

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

COPY

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronic Patent Application Fee Transmittal

Application Number:	10008955			
Filing Date:	07-Dec-2001			
Title of Invention:	<div>COPY</div> Natural killer cell lines and methods of use			
First Named Inventor/Applicant Name:	Hans Klingemann			
Filer:	Christine W. Trebilcock/Dennis Ditzenberger			
Attorney Docket Number:	06-129 PCT/US/CIP			
Filed as Small Entity				
Utility under 35 USC 111(a) Filing Fees				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with \$0 paid	2253	1	555	555

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
Request for continued examination	2801	1	405	405
Total in USD (\$)				960

COPY

COPY

**REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)**

Application Number	10008955	Filing Date	2001-12-07	Docket Number (if applicable)	06-129 PCT/US/CIP	Art Unit	1644
First Named Inventor	Hans Klingemann			Examiner Name	Ronald B. Schwadron		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application. Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

☒ Enclosed

☒ Amendment/Reply

☐ Information Disclosure Statement (IDS)

☒ Affidavit(s)/ Declaration(s)

☒ Other Submission of Amendment to Sequence Listing

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 032026

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

Doc code: RCEX

Doc description: Request for Continued Examination (RCE)


PTO/SB/30EFS (09-08)

Approved for use through 10/31/2008. OMB 0851-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

COPY

Signature of Registered U.S. Patent Practitioner			
Signature		Date (YYYY-MM-DD)	2008-10-15
Name	Christy Rothwell	Registration Number	55936

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

COPY

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Hans Klingemann

Serial No. 10/008,955

Filed: December 7, 2001

Art Unit: 1644

Patent Examiner: Ronald B. Schwadron

Attorney Docket No. 06-129PCT/US/CIP

Confirmation No.: 5420

COPY

NATURAL KILLER
CELL LINES AND METHODS
OF USE

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

October 15, 2008

SUBMISSION OF
AMENDMENT TO SEQUENCE LISTING

This communication concerns the above-identified application.

Remarks begin on page 2 of this paper.

A paper copy of the Amended Sequence Listing is provided in Appendix A following page 4 of this paper.

A computer-readable format of the Amended Sequence Listing is filed herewith.

REMARKS

COPY

Amendment to the Sequence Listing

Applicant has amended the Sequence Listing to include "reverse primer" in SEQ ID NO: 2, section <223>, and has further amended the sequence listing to correct an inadvertent typographical error in <150> to read "PCT/US98/08672" to correctly identify the claim of priority to the International Application. Support for the amendments is found in the Substitute Specification filed on October 5, 2007, at least at pages 53 and 1, respectively. The amended Sequence Listing contains no new matter.

Applicant submits herewith a paper copy of the amended Sequence Listing in Appendix A following page 4 of this paper along with a computer-readable copy of the amended Sequence Listing. The copy in computer readable form is the same as the substitute copy of the Sequence Listing.

Conclusion

Applicant respectfully submits that the application and claims are in condition for allowance. Accordingly, reconsideration and allowance of all claims are respectfully requested.

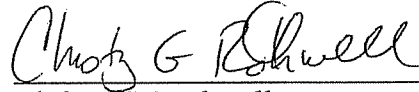
Applicant would appreciate the courtesy of a telephone call should the Examiner have any questions or comments with respect to this submission for purposes of efficiently resolving same.

COPY

The Commissioner is hereby authorized to charge Deposit Account No. 03-2026 for any fees associated with this submission.

Respectfully submitted,

By



Christy G. Rothwell

PTO Registration No. 55,936

Cohen & Grigsby, P.C.

625 Liberty Avenue, 5th Floor

Pittsburgh, PA 15222-3152

(412) 297-4900

#1390820v1

APPENDIX A

COPY

ZellerX CIP_ST25.txt
SEQUENCE LISTING

COPY

<110> Klingemann, Hans
<120> Natural Killer Cell Lines and Methods of Use
<130> 06-129 PCT/US/CIP
<140> 10/008,955
<141> 2001-12-07
<150> 09/403,910
<151> 1999-10-27
<150> PCT/US98/08672
<151> 1998-04-30
<150> 60/045,885
<151> 1997-04-30
<160> 2
<170> PatentIn version 3.5
<210> 1
<211> 20
<212> DNA
<213> Artificial Sequence
<220>
<223> primer oligonucleotide based on human sequence
<400> 1
caactcctgt cttgcattgc

<210> 2
<211> 19
<212> DNA
<213> Artificial Sequence
<220>
<223> reverse primer oligonucleotide based on human sequence
<400> 2
gcatcctggt gagtttggg

20

19